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AN INVESTIGATION OF THE THERAPEUTIC PROPERTIES OF PENICILLIN

A REPORT TO THE MEDICAL RESEARCH COUNCIL

BY

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A REVIEW OF THE WORK OF A PENICILLIN THERAPEUTIC RESEARCH UNIT

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It is now common knowledge that the discovery of penicillin by Fleming (1929) and its extraction in more concentrated form by Chain and Florey were followed by clinical trials in Oxford by Florey and his collaborators, from which it became clear that penicillin is a therapeutic agent of a new type and extraordinary powers (Chain *et al.*, 1940; Abraham *et al.*, 1941; Florey and Florey, 1943). When further, although very limited, supplies of penicillin became available from commercial sources the Medical Research Council was entrusted with its distribution for extended therapeutic study. The Council's Penicillin Clinical Trials Committee, established in March, 1943, allocated supplies to four main centres, as well as to a number of other institutions where smaller quantities were used for specific purposes. This and succeeding papers constitute a report from one of these centres on work which has now been in progress for rather less than a year.

At this stage the foundations of penicillin therapeutics had already been well laid by the Oxford workers, and the following is a short summary of what was known of its properties. Penicillin itself is highly unstable, but its calcium and sodium salts are relatively stable, and it is in one of these forms that the substance is used therapeutically. All preparations hitherto available have been impure, containing often only a small percentage of true penicillin: dosage is therefore not calculated by weight, but in terms of Oxford units, this being a measure of bacteriostatic power assessed by comparison with a standard product.

Penicillin has three fundamental properties on which its action in the body depends. The first is enormous antiseptic power: even when diluted a millionfold or more it will still completely prevent the growth of certain bacteria. The second is almost complete indifference to the medium in which it acts: other antiseptics with comparable activity in water or broth lose most of this activity when brought into contact with the protein and cellular constituents of body fluids, but penicillin acts as well in serum, blood, or even pus as in broth. Thirdly, it is almost completely non-toxic to the body as a whole, and, so far as is known, to any of its constituent cells: only enormous concentrations, far in excess of those required for action on bacteria, interfere with the activity of leucocytes or any other cells hitherto studied from this standpoint. These are of course the three properties which have long been postulated, without any serious expectation of ever finding them combined to this degree in one substance, as those of the ideal antiseptic.

It is of the first importance to recognize that this action is exerted only against certain bacteria; others are highly resistant to it, and penicillin has for years been used by Fleming (1932) as a constituent of selective culture media. Susceptible bacteria are almost all Gram-positive, the chief exceptions to this rule being the gonococcus and meningococcus. The most important of the susceptible Gram-positive species are the three main pyogenic Gram-positive cocci—*Staphylococcus aureus, Streptococcus pyogenes,* and *Pneumococcus*—and it is noteworthy that whereas staphylococcal infections are far more resistant than haemolytic streptococcal infections to sulphonamides, they are almost equally susceptible to penicillin treatment. The gas-gangrene group (including *Cl. oedematiens,* which is relatively sulphonamide-resistant), *B. anthracis, C. diphtheriae,* some strains of *Strep. viridans,* and *Actinomyces* have also been found susceptible *in vitro.* More or less resistant species include almost all Gram-negative bacilli—the typhoid-dysentery group and coliforms generally, *Proteus, Ps. pyocyanea,* the genera *Haemophilus* and *Brucella,* and *Strep. faecalis* and *Myco. tuberculosis.*

Systemic or Local Treatment

Penicillin injected intravenously or intramuscularly circulates in the blood and thus reaches every part of the body, but, owing to the rapidity of renal excretion, heavy dosage is necessary to maintain an adequate concentration. This method of administration is obviously necessary in septicaemia, and has been found so in some local but extensive or inaccessible infections. The dose required for an adult is about 120,000 units daily, and treatment may have to be continued for a week or longer. Thus a million units or more may be given to a single case, whereas a second method of use—the application of penicillin in some form locally to the lesion—may be fully successful and employ only a few thousand units. Owing to the present imperative need for economy, it is therefore a major rule of penicillin treatment to use local application whenever this will suffice. The technique of local application has much to do with success: many new methods have been devised, and further improvements may yet be achieved.

The Choice of Cases for Treatment

The impulse of anyone with penicillin at his disposal for the first time is to use it for treating those conditions in which it most clearly excels every other remedy, and particularly for saving life. Staphylococcal septicaemia, and septicaemia or meningitis due to a sulphonamide-resistant *Strep. pyogenes* or pneumococcus, are probably the foremost conditions in which penicillin may alone be capable of saving life, and these were among the subjects of therapeutic study approved by the Penicillin Clinical Trials Committee at its first meeting. It soon became evident that the supplies available were quite inadequate

for treating all such cases referred to us, and it has now been decided that cases of staphylococcal septicaemia will not be accepted for treatment. It is one thing to use penicillin to the best advantage in accordance with existing knowledge, and quite another to use it in order to expand that knowledge. The second of these objects was clearly the purpose of our work, and cases are therefore being accepted only if they appear likely to further it. Even were one to resolve to use a limited stock of penicillin for purposes of well-ascertained value, the choice of cases involves decisions of the most difficult kind. As Florey and Williams (1944) have recently shown, 500,000 units of penicillin suffice for the local treatment of over 100 cases of infections of the hand, with an immense gain in rapid restoration of function. The same quantity would cure five cases of sulphonamide-resistant gonorrhoea, and the demand for this purpose may be insistent if the patients are key Service personnel needed in a forthcoming offensive (Report to War Office, 1943). On the other hand, this quantity of penicillin would be inadequate for the treatment of a single case of septicaemia.

The policy at this centre, although defined only after our work had been in progress for some time, is at present to explore further the possibilities of local treatment in as many directions as possible, and to confine systemic treatment, as a general rule, to early cases of infection of bone—a difficult field in which further study seems desirable. This policy may be changed if new circumstances appear to require it. We have naturally been influenced by the availability of clinical material on the spot, and the special Orthopaedic, Thoracic, and Facio-maxillary and Plastic Units at Hill End Hospital, where most of this work has been done, have provided many of the cases.

One hundred and ninety-eight patients were treated by the local application of penicillin and 18 by systemic administration. Most of them fell into the following clearly defined groups: skin diseases (75 cases), wounds of the skin and soft tissues (70 cases), breast abscesses (15 cases), infections of the mandible (20 cases), and other infections of bone (34 cases). These various groups are described in the series of articles that follows, written by those who were responsible for the treatment of the patients concerned. A few cases could not be placed in any of these groups, and as in several the results of treatment are of interest, these will be described briefly.

The local application of penicillin to the eye in three cases of iritis gave results which strongly support the suggestion that penicillin may diffuse through the cornea in amounts which are of therapeutic significance. The first was a patient with gonococcal iridocyclitis. He was apparently cured after ten days' treatment, but later relapsed. A further course of treatment lasting five days was again successful, and there has been no further relapse. The second and third cases were of iritis of unknown aetiology, and both were apparently cured within a week. It would be unwise to draw any definite conclusions from so small a series, but in the light of previous experience with this type of infection it seems extremely probable that the results obtained were due to the diffusion of penicillin through the cornea. Three cases of conjunctivitis—two chronic, one acute—were also treated by local application with outstanding success. The observations on iritis were made by our colleague Major Seymour Philps.

In two cases of chronic otitis media instillation of penicillin solution was associated with the disappearance of penicillin-sensitive organisms from the discharge, and apparent clinical improvement. In both, however, the condition relapsed within a day or two of cessation of treatment. In one case of acute bilateral otitis media recovery appeared to be hastened, and was complete after seven days of treatment.

Sixteen patients with acute empyemata were treated by the aspiration of pus and replacement with penicillin solution. One or two intrapleural injections of from 15,000 to 30,000 units were sufficient to sterilize the pus; but to obtain a good functional result subsequent drainage of sterile pus was usually found to be necessary. Details of these cases will be published at a later date by Mr. Tubbs, who is responsible for this part of our investigations.

Seventeen patients were given penicillin by one or other of the systemic routes. Nine of them were cases with bone infection, and these are described in one of the articles which follow. Of the other 8 cases some were treated during the early stages of our investigations, before a clear policy was established of the lines along which research could most profitably be directed. Others were chosen because the prognosis without penicillin appeared to be hopeless, and the trial of new methods of administration was therefore justified. Four were suffering from staphylococcal septicaemia. In all of them the infecting organism was a coagulase-positive *Staph. aureus* which was penicillin-sensitive. The two cases which were first treated were critically ill with multiple abscesses and yet no leucocytosis. In both adequate bacteriostasis in the blood was maintained by the daily administration of approximately 120,000 units, and the blood cultures remained negative. Although a total of 2 million units in 23 days was given to the first and 3 million units in 18 days to the second, both patients died. On post-mortem examination both were found to have multiple abscesses which contained living staphylococci. In both a large abscess was present under the muscles of the thigh; in the first case this contained about three pints of pus, and in the second about one pint.

In the third patient, who was also critically ill with staphylococcal septicaemia, systemic administration was combined with energetic local treatment; abscesses in the arm and leg and a suppurative pericarditis were drained and penicillin solution instilled. The patient made a complete recovery.

The fourth case of staphylococcal septicaemia had various transitory signs which suggested cerebral abscess, though location of it was not possible. He appeared to respond well to systemic treatment, which cured the septicaemia, but definite localizing signs subsequently appeared, and a subdural abscess and a cerebral abscess were successfully drained. Both abscesses contained *Staph. aureus*.

Thus of 4 cases of staphylococcal septicaemia 2 were fatal. One lesson to be learned from the two fatal cases is that penicillin does not replace surgical drainage, and when pus forms in any quantity it must be evacuated. They may be interpreted in a more general way as indicating that penicillin cannot be expected to save every case of staphylococcal septicaemia; we believe that the 100% recovery rate reported by Florey and Florey (1943) is more than will usually be achieved. To judge by other reports, the prognosis can be affected adversely in several ways: the development of an endocarditis, which was found post mortem in one of these cases, is a particularly unfavourable feature.

The fifth case was one of bilateral sulphonamide-resistant streptococcal pneumonia of six weeks' duration. The outlook appeared to be hopeless, but the patient recovered after 750,000 units of penicillin had been given by the intravenous route.

The sixth case was one of actinomycosis of the chest wall and lung. The sensitivity of the organism was about one-fourth of that of the standard Oxford staphylococcus. 700,000 units of penicillin were given over a period of seven days. The patient died at the end of this period from *Ps. pyocyanea* septicaemia and pyaemia. (The source of infection was the intravenous drip.) Necropsy showed extensive pulmonary actinomycosis. The fungus colony in section stained poorly and appeared to be disintegrating. This may have been the effect of treatment.

The seventh case was that of an infant with staphylococcal peritonitis and perinephric abscess. The outlook appeared quite hopeless, and a drip containing penicillin was given into the marrow of the tibia. The patient died, and a post-mortem examination showed no evidence of damage to the marrow at the site of injection.

The eighth patient was a child with pneumococcal meningitis associated with bilateral infection of the mastoids, which had been drained. 800,000 units of penicillin were given systemically and 30,000 units by cisternal, ventricular, or lumbar puncture. There has now been no evidence of infection for two months, but the child remains semi-comatose, and it seems likely that, although penicillin has affected a "cure," there has been permanent damage to the brain. We understand that others have had similar experiences in the treatment of meningitis with penicillin. The rapidity with which penicillin may pass from the cisterna magna to the ventricles of the brain was well illustrated in this patient: one and a half hours after 5,000 units had been introduced by cisternal puncture the ventricular fluid inhibited the growth of the standard staphylococcus in a dilution of 1 in 40.

The cases which have been described form a small and relatively unimportant part of the work of our centre. Much more was learned from the series of carefully chosen cases which are described in the articles which follow.

The penicillin used throughout these investigations was supplied by the Therapeutic Research Corporation through the Medical Research Council and Ministry of Supply.

We wish to express our indebtedness to Prof. H. W. Florey and his colleagues at Oxford, who at the outset of the work of the Penicillin Clinical Trials Committee placed their unique experience at our disposal and thus enabled these studies to be begun.

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EXPERIENCES IN THE SYSTEMIC ADMINISTRATION OF PENICILLIN

BY

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Systemic treatment depends for its success upon the maintenance of an adequate concentration of penicillin in the blood stream. This may be achieved by either continuous drip transfusion or intermittent injection. Neither of these is wholly satisfactory.

Continuous Intravenous Drip Transfusion

30,000 units of sodium penicillin were dissolved in 1 pint of fluid; transfusion of this amount in 6 hours was considered a suitable initial rate for adults. This dose of penicillin was reduced in the case of younger patients, and subsequent dosage was controlled by blood-titre estimations. The fluid intake was regulated according to the patient's needs. Penicillin was usually dissolved in 4% dextrose in 0.18% saline, but was sometimes added to blood for transfusion. The standard practice was to expose the vein and insert a cannula. A needle was used where it was likely that treatment would be of short duration.

Details of the cases treated by this method are given in Table I. The word "thrombosis" in the table refers to cases in which the drip stopped without rise of temperature or regarded as an indication for stopping the transfusion without delay. Though impurity of the penicillin probably was largely responsible for this complication, the evidence in Table I does not incriminate any particular batch. The condition generally subsided very rapidly when the transfusion was discontinued, but one case (H. R., who was suffering from extensive thoracic actinomycosis) died of a septicaemia due to *Ps. pyocyanea*, with the primary focus of infection at the site of the transfusion.

Impairment of renal function may lead to retention of penicillin in the blood, so that an adequate concentration may be maintained with much smaller doses (Rammelkamp and Keefer, 1943). This was illustrated by the following estimations of blood titre made in the case of a woman (Case N. M. 3) whose urine contained many red blood cells and granular casts and in whom the blood urea was 56 mg. per 100 c.cm. She had been receiving 30,000 units by intravenous drip transfusion six-hourly. Administration was stopped at 8.15 a.m. and blood removed at intervals subsequently:

Time	Dilution of Serum producing Complete Bacteriostasis	Dilution of Serum producing Partial Bacteriostasis
8.15 a.m.	1 in 32	1 in 64
9.45	1 in 32	1 in 64
11.15	1 in 8	1 in 16
12.45 p.m.	1 in 4	1 in 8
2.15	1 in 4	1 in 8
3.43	1 in 4	1 in 8
5.15	1 in 4	1 in 8
6.45	1 in 4	1 in 8

A specimen taken at 9.45 p.m. showed no bacteriostasis in any dilution.

TABLE I.—*Administration by Intravenous Drip Transfusion*

Case	Age	Character of Veins	Batch	Units Given	Medium	Method	Site	Duration in Hours	Reason for Stopping
S.H.	44	Good	TRC1	603,000	N. saline	Cannula	L. ankle	72	Adequate dose given
N.M. (1)	27	,,	TRC3M	180,000	Dextrose-saline	,,	R. ankle	24	Thrombosis
N.M. (2)	27	,,	,,	1,095,000	Dextrose-saline, dextrose, blood	,,	L. ankle	192	,,
N.M. (3)	27	,,	,,	782,250	Blood, dextrose-saline	,,	L. forearm	173	Death
N.W. (1)	31	Moderate	,,	408,750	N. saline, dextrose-saline, dextrose	,,	R. ankle	50	Thrombosis
N.W. (2)	31	,,	,,	405,000	Dextrose	,,	L. ankle	79	,,
N.W. (3)	31	,,	,,	135,000	Dextrose-saline	,,	L. forearm	27	,,
K.P. (1)	12	Good	R1	237,000	,,	,,	L. ankle	48	Thrombophlebitis
K.P. (2)	12	,,	,,	84,000	,,	Needle	L. arm	16	,,
K.P. (3)	12	,,	TRC3M	278,000	,,	,,	R. arm	63	,,
K.P. (4)	12	,,	,,	80,000	,,	,,	L. arm	18	Thrombosis
E.D. (1)	25	,,	,,	232,500	,,	Cannula	L. ankle	48	Thrombophlebitis
E.D. (2)	25	,,	,,	510,000	,,	,,	R. ankle	112	,,
P.B. (1)	10	,,	,,	375,000	,,	,,	R. forearm	158	,,
P.B. (2)	10	,,	,,	364,000	,,	,,	L. forearm	145	,,
J.P. (1)	38	Moderate	TRC8	710,000	,,	,,	L. ankle	142	,,
J.P. (2)	38	,,	,,	357,000	,,	,,	L. forearm	72	Adequate dose given
F.S.	42	,,	,,	496,250	,,	,,	R. ankle	100	Thrombophlebitis
H.R.	51	Good	R1, TRC3M	733,750	,,	,,	R. ankle	146	,,
P.R. (1)	14	,,	TRC10	57,500	,,	,,	L. ankle	23	Pulled out
P.R. (2)	14	,,	,,	207,500	,,	,,	L. forearm	91	Thrombophlebitis
E.W.	58	Poor	TRC10, TRC12a	571,670	,,	,,	L. forearm	126	,,
J.B. (1)	14	Good	TRC10	267,300	Blood, dextrose-saline	,,	L. elbow	100	,,
J.B. (2)	14	,,	,,	40,000	Dextrose-saline	Needle	R. elbow	14	Adequate dose given
R.P. (1)	12	,,	,,	277,500	Dextrose-saline, blood	,,	L. elbow	84	Thrombosis
R.P. (2)	12	,,	,,	7,500	Dextrose-saline	,,	R. elbow	3	,,

TABLE II.—*Administration by Intramuscular Injection*

Case	Age	Character of Muscles	Batch	Units Given	Duration in Days	Vol. of Inj. in c.cm.	Reaction of Patient	Local Inflammation
S.H.	44	Fair	TRC1	1,323,400	20	10, 2.5	Well tolerated	Slight
N.W. (1)	31	,,	TRC3M	675,000	5½	10, 5	Strongly objected to	Marked
N.W. (2)	31	,,	,,	900,000	13	5	,, ,,	,,
K.P.	12	Poor	TRC3M, R1	352,000	8	5, 4	,, ,,	Slight
J.P.	38	Good	TRC8	375,000	4	5	Strongly objected to; further injections refused	Marked
F.S.	42	,,	,,	900,000	7½	5	Well tolerated	,,
H.R.	51	Fair	TRC10	105,000	3	2·5	Tolerated (comatose)	Absent
J.H.	10	Poor	,,	740,000	11	2	,,	Slight
D.V.	24	Good	,,	1,180,000	11	2·5	Well tolerated	,,
P.R.	14	Poor	,,	232,500	5	1·5	Objected to	,,
E.W.	58	Fair	,,	502,500	8	2	Strongly objected to	,,
D.P.	6 wks.	Poor	,,	28,000	5	1·5	Well tolerated	Absent

evidence of active inflammation. It will be seen that a number of these transfusions were stopped prematurely, most commonly through the development of thrombophlebitis. This occurred after varying periods, but on an average after about 100 hours. In spite of inflammation extending up the vein, the fluid sometimes continued to drip; thrombophlebitis should, however, be

Calcium penicillin was administered intravenously in one case (E. W.), first as a single injection, and afterwards by continuous drip transfusion for 24 hours. There were no ill effects, no evidence of delayed excretion when compared with a control dose of sodium salt, and no rise in serum calcium level.

The advantages of continuous intravenous transfusions were: (1) continuous maintenance of adequate blood titre; (2) combination with parenteral fluid administration, which was sometimes indicated.

The disadvantages were: (1) frequent and painful thrombophlebitis; (2) the method was expensive of veins, especially when these were cannulated and made useless for future occasions.

Intermittent Intramuscular Injection

A dose of 15,000 units 3-hourly was adopted as the standard adult dose. Table II shows a series of courses of these injections. It will be seen that the reactions of the patient, both general and local, varied considerably from case to case. The cases, which are arranged chronologically in the table, show that on the whole the later batches of penicillin were better tolerated. Not only the degree of impurity of the preparation, but also the condition of the patient and the volume of individual injections, appeared to have a bearing on toleration of the method.

The mere dislike of an intramuscular injection of any kind repeated every three hours, day and night, accounted for strong subjective reactions against the method even when inflammation was slight. There was always pain after the injections, even when these were "well tolerated." This lasted for varying periods, and in the severer instances until the next injection. Pyrexia in patients otherwise afebrile was noted in two cases (J. P. and F. S.); the former felt and looked ill.

The advantage of this method was its simplicity. The disadvantages were: (1) Pain, especially if injections had to be confined to one site. (2) Disturbance of the patient. The ruthless regularity of a painful injection every three hours was more than several of our patients could bear. (3) The rise and fall in blood titre (perhaps not a disadvantage).

Drip Transfusion into Bone Marrow

It was felt that this route should be tried as a possible alternative to the two routes already considered. Five such transfusions were set up, the method described by Tocantins and O'Neill (1941) being used. The details of these are given in Table III. Dextrose-saline was employed in all of them.

TABLE III.—*Administration by Drip Transfusion into Bone Marrow*

Case	Age	Batch	Units Given	Site	Duration in Hours	Reason for Stopping
J.H.	10	TRC10	46,000	Sternum	9	Blockage
D.P. (1)	6 wks.	,,	4,500	L. tibia	9	,,
D.P. (2)	6 ,,	,,	22,500	R. tibia	48	,,
D.V.	24	,,	30,000	Sternum	2	,,
P.R.	14	,,	25,000	R. femur (site of infection)	7	Leakage

It was most difficult to run in more than one pint through the sternum. The stoppages at this stage cannot be attributed to the penicillin; rather were they due to difficulties inherent in the method itself. Tibial transfusion was employed on two occasions. The second transfusion, although it lasted 48 hours, could not be made to run at a rate adequate to introduce all of the required dose. There are bound to be difficulties in the systemic treatment of infants; the method therefore was encouraging enough to warrant further trial. Samples of bone marrow from sternum and tibia were examined before and after transfusion, and showed no changes which could be ascribed to penicillin.

In Case P. R., a patient with osteomyelitis of the upper end of the femur, a sternal needle was introduced (at exploratory operation), through a drill-hole, into the medulla of the infected bone. A drip transfusion was subsequently established, using this route, but the fluid leaked back along the track of the needle, and it was therefore discontinued. The needle was left in position and used for four-hourly injections, as a result of which an adequate blood concentration was obtained. Some local pain was felt. The value of this method was doubtful.

Continuous Intramuscular Drip Transfusion

In view of the disadvantages of the foregoing methods, and at the suggestion of Dr. Valentine, we employed intramuscular transfusions on 6 occasions. The same dose of penicillin was used as for the intravenous route. The medium employed was in all cases dextrose-saline. It was found that two pints of fluid per 24 hours was a suitable rate of flow, though Billimoria and Dunlop (1940) stated that larger amounts of fluid can be given if that be the object of the transfusion. An ordinary intramuscular needle was used with an improvised wire frame for supporting it in position. The results are recorded in Table IV.

TABLE IV.—*Administration by Drip Transfusion into Muscle*

Case	Age	Batch	Units Given	Pints per 24 Hours	Site	Duration in Hours	Reason for Stopping
P.R.	14	TRC10	408,750	3, 2	Outer side of L. thigh	164	Adequate dose given
J.B. (1)	14	,,	35,500	2	,,	20	Leakage
J.B. (2)	14	,,	518,000	2	,,	237	Local abscess
A.S.	19	,,	383,000	3, 2	Outer side of R. thigh	80	Pulled out
R.P. (1)	12	,,	348,750	2	Outer side of L. thigh	105	Local abscess
R.P. (2)	12	,,	135,000	2	Outer side of R. thigh	38	Adequate dose given

It will be observed that all the patients were young. We found that the daily administration of three pints by this route was very apt to cause leakage back along the track of the needle. Restriction of the intake to two pints by transfusion and to three pints by mouth stopped this satisfactorily.

Local abscesses around the site of the needle formed in two cases. Culture of the pus produced a growth of coliform bacilli. In the case of J. B. the blood titre fell so that no detectable penicillin was present; absorption from the abscess cavity was presumably very slight. It should be possible to avoid this undesirable complication by improved methods of anchoring the needle, prevention of any leakage, and removal of the needle at the first signs of any inflammation. Possibly, also, elevation of the limb would help by avoiding stasis; the abscess in R. P. was at the most dependent part of the thigh rather than centred round the needle. These two abscesses had to be opened, but they healed in about three weeks.

The method was almost pain-free, and swelling of the thigh was slight provided the rate of drip was kept constant. Improvements in technique are now being investigated, with encouraging results.

The advantages of the method are: (1) continuous maintenance of adequate blood titre; (2) comparative freedom from pain; (3) availability of numerous sites for transfusion, poor musculature being apparently no bar to the method.

The disadvantages are: (1) tendency to local infection and abscess formation; (2) possibility of having to restrict total fluid intake.

Summary

The complications which may arise when penicillin is administered by intramuscular injection and by continuous intravenous and intramuscular drip transfusion are described. Each method has its advantages and disadvantages, and may be the best for any particular case.

It is possible that drip transfusion into the bone marrow of the tibia may be of value in the administration of penicillin to infants.

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The Universities' Federation for Animal Welfare (UFAW), in response to a demand, has begun the compilation of a handbook on the care and management of the smaller laboratory animals. The secretary is Dr. F. Jean Vinter, 284, Regent's Park Road, Finchley, N.3. Various sections of the book are being drafted by research workers having appropriate special knowledge, but the Federation wishes to supplement the drafts with information derived from a wide range of sources. It is accordingly sending a list of subjects to all licencees under the Cruelty to Animals Act, 1876. Inquiries are invited from non-licence-holders, some of whom might help in this undertaking. The work as a whole will be submitted before publication to a small number of eminent men of science.

SURGERY AND PENICILLIN IN MANDIBULAR INFECTION

BY

RAINSFORD MOWLEM, F.R.C.S.

This series of 21 cases of infection in connexion with bone is too small to justify detailed analysis, but it may help to clarify the part which penicillin can be expected to play. The cases fall into two groups. In the first, infection has been anticipated after surgery. The use of penicillin has been withheld until the presence of sensitive bacteria has been shown. This has been done in an attempt to evaluate the effects of penicillin under conditions of bacteriological control, and has sometimes caused an undesirable delay. The second group comprises cases of well-established bone infection, all of which have been subjected to full bacteriological investigation, and all of which have been treated by radical surgery and penicillin.

One other case is included for the moral it points:

Case 1331.—Soldier aged 53. Presented a two-months-old sinus in the iliac crest, with induration of the surrounding tissues. Haemolytic streptococci ++; *Staph. aureus* ++. Penicillin 1,000 units was injected daily for ten days, with improvement in the surrounding soft tissue but no change in the sinus or its bacteriology. At operation a small sequestrum was found in a cavity lined by fibrous tissue, about 3/8 in. thick.

It is not to be expected, in such circumstances, that even if sterility can be obtained it will automatically be followed by healing. The fibrosis and its resultant avascularity are the determining factors, and not the infection, and this will be true of many established bone infections.

Group I

This consisted of 4 post-operative cases, in all of which infection was either anticipated or was causing early reaction. In all of them immediate bacteriological and clinical control was obtained, and was followed by satisfactory healing.

Case 1629.—Soldier aged 31. Sept. 13, 1943: Resection of the left side of the mandible from the canine tooth to the temporo-mandibular joint, for an infected multilocular cyst of the whole area. Nov. 8: Chip bone grafting for complete restoration, in spite of a persistent sinus into the mouth. A penicillin tube was inserted along the upper margin of the grafts. Nov. 11: Cheek puffy and tender. Fluid withdrawn from the tube shows *Staph. aureus* ++. Penicillin 1,000 units in 1 c.cm. injected daily. Nov. 15: The local signs of infection had disappeared, and aspirated fluid was sterile. The next day penicillin was discontinued, and recovery was complete.

It is felt that penicillin contributed very materially to a speedy and uncomplicated convalescence.

Two other bone-graft cases—one with exposure to the surface, and the other with a sinus into the mouth—were treated. In the former satisfactory healing was obtained, but in the latter a few chips of the graft were lost, though the greater number survived. This loss may have been due either to the late and inefficient application of penicillin or to inadequate drainage.

In the fourth case most of the right side of the mandible was resected for an odontoma. In spite of drainage the resultant cavity filled with blood clot and on the sixth day swabs showed haemolytic streptococci ++, *Staph. aureus* ++, coliforms +. 6,000 units of penicillin were injected in the next three days, and thereafter penicillin cream (400 units per gramme) was applied to the drainage opening. On the 12th day the wound was dry and healed.

In this series, therefore, the evidence points to early bacterial control with consequent normal healing, and no local deleterious effects have been seen.

Group II

This comprised 16 cases of osteomyelitis of the mandible. In all of them infection has been gross and well established, and penicillin has been used in conjunction with radical surgery. Since surgery, other than drainage, is not often adopted, it may clarify the position to state the considerations on which it is based.

Osteomyelitis of the mandible is a relatively rare condition which may—especially in children—arise from blood-borne infection, but which more frequently is preceded by the extraction of teeth. The cause of the former condition is clearly understood, but the latter type is commonly attributed to less well defined factors. "Diminution of local immunity" and "specific organismal infection" have both been suggested. The latter condition appears to be incapable of proof, and it has so far been impossible to recover from the infected mandible any organisms which can be shown to differ from those present in the normal mouth. In this series the following organisms in various combinations have been encountered: haemolytic streptococci and *Staph. aureus*, both aerobic and anaerobic, pneumococci, *Strep. viridans, H. influenzae*, coliform bacilli, and a host of lesser Gram-negative organisms. These may all occur in the normal mouth as well as in the infected jaw, and if their presence were the important factor one might expect massive bone infection to follow almost every dental extraction.

"Local low immunity" is meaningless if it envisages a condition in which otherwise normal tissues become incapable of resisting bacterial invasion by reason of some unspecified cellular change. At the same time there must be some factor which determines whether or not a fairly constant type of mouth infection shall invade the bone. It is suggested that this factor is the local vascular system, which is the key to the mobilization of the defence mechanism. If the potent factor is a vascular one, it is further suggested that thrombosis is the primary disaster. This may be caused either by direct trauma to the inferior dental vessels during the removal of a tooth or by the central extension of thrombosis in the vessels supplying either a tooth root or the surface structures. Occlusion of the main vessels will create a large central area of bone of reduced vitality in which the secondary bacterial invasion is incapable of being withstood. It is obvious that the further back along the vessel this thrombosis extends the greater will be the disaster, and clinical findings tend to bear this out. Though thrombosis is often seen at operation, it is almost impossible to say whether it has preceded or followed the infection, but the probability of its being the primary cause is evidenced by the following:

(*a*) Mandibular bone infection is rare after the extraction of incisor teeth, and in this area it is usually localized. As one goes further back along the tooth-bearing ridge both the probability and the severity of infection increase. This variation would seem to be dependent upon anatomical consideration of the vascular distribution.

(*b*) The extraction of deciduous teeth is seldom followed by infection, not because of any difference in the bacterial flora of the mouth in early life, but because damage to the inferior dental vessels is unlikely. The roots of children's teeth are not in close approximation to the vessels, and may be separated from them by the upgrowing secondary dentition.

(*c*) Osteomyelitis of the superior maxilla following dental extractions is almost non-existent. The blood supply of this bone is segmental and vertical, and is incapable, in its periphery, of complete occlusion. The bacteriological state of the mouth must just as often be as potentially dangerous as in extractions of the lower teeth, but the probability of infective invasion remains infinitely remote.

Once medullary infection is established it passes through an acute primary phase to become a chronic condition. This is due partly to its enclosed position, but to a greater extent to the density of the surrounding bone. This bone, because of its relative avascularity, is incapable of rapid inflammatory response, and is often extruded as a sequestrum after many months. The problem is to remove the devitalized, thrombosed, and infected medullary bone, to eliminate that part of the dense cortical bone which cannot resist the spreading infection, and to leave behind only those areas which have an adequate blood supply to enable them first to deal with residual organisms and later to regenerate new bone.

Operation therefore consists in the subperiosteal excision of the lower border of the bone, together with the outer plate and all the infected medullary area. This frequently leaves a lingual plate less than 1/8 in. in thickness and only about 3/8 in. in vertical extent (Fig. 1). It has sometimes been argued that the exposure of uninfected bone by such a clearance would result in further osteomyelitis. This is not the case in such virulent infections as are encountered in acute mastoiditis, and does not seem to occur in the mandible if only vascular bone is left behind. Until

the advent of penicillin the overlying soft tissues of the cheek were then packed away from the bone and the cavity allowed to granulate from its depth. The sulphonamide group did much to control infection, but packing still seemed necessary.

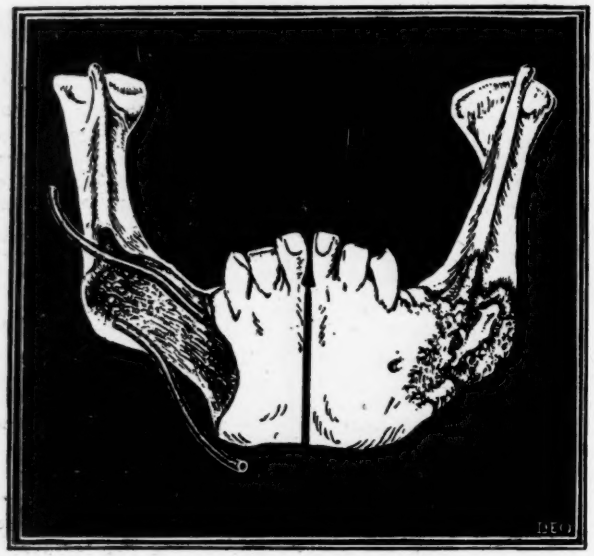


FIG. 1.—Schematic representation of osteomyelitis on the left side and the type of excision and the site of penicillin tubes on the right side.

When penicillin became available it was decided to continue this radical surgery with closure of the soft tissues. This has three advantages: (*a*) The soft tissues of the cheek may be closely approximated to the underlying bone, and can be expected to contribute to vascular ingrowth. (*b*) The closed cavity not only excludes secondary infection but also retains the penicillin, which is thus permitted to exercise almost continuous action. (*c*) Primary instead of delayed healing is obtained. Such a result in established bone infection presents an old and time-consuming problem in an entirely new light.

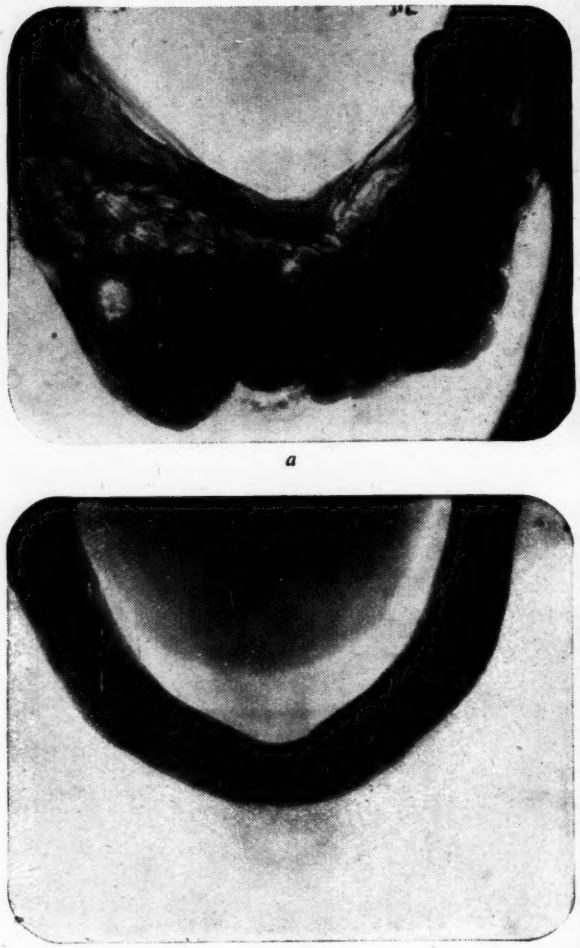
The technique which has been used in the cases here reported therefore consists in extensive surgical removal of bone as described above. During operation, bacteriological swabs taken from the centre of the infected area are sent for culture and penicillin-sensitivity test. Two small-bore tubes are then inserted through separate stab wounds—one to run along the upper border of the residual bone and the other along the lower edge. The wound of access is then closed without drainage even though it has extended through an abscess cavity.

Within about 18 hours a bacteriological report is available and penicillin treatment is begun. The usual dosage is now 1,000 units in 1 c.cm. into each tube every 24 hours. Immediately before each injection the cavity is aspirated through the penicillin tubes, and any resultant fluid sent for bacteriological investigation and penicillin-inhibition test. Treatment is continued until the wound is healed—on the average, ten days.

There is considerable similarity between all the cases in the group, and only two—one recent and one old—will be quoted at length.

Case 1628.—Soldier aged 21. May 1, 1943: Reported sick with a boil on the chin and swelling of the left side of the neck. Admitted to a hospital on May 12 with the original boil healed, but with an increase in the swelling of the neck. This was incised and three teeth were removed. Transferred to the Plastic Unit, July 9. He then presented a generalized swelling of the mental region with an extension to the left side. There were several recent scars and a discharging sinus in the neck. In the mouth, pus was welling up through two tooth sockets and through several fistulae. July 12: Operation. Extraction of 54321/1237. The mandible was then exposed from below and the lower margin removed almost as far back as the angle on each side. Excision of the full vertical extent of the outer plate revealed necrotic tissue occupying the medullary space. This also was removed, leaving a thin shell of normal bleeding lingual lamina. Two penicillin tubes were inserted and the wound closed. Finally the gum at the site of the extracted teeth was trimmed and sutured, thus completely closing the cavity. July 13: Bacteriological report on the swab taken at operation shows penicillin-sensitive *Staph. aureus* +++. Penicillin 1,000 units in 1 c.cm. injected into each tube twice daily. July 21: Aspirated fluid has been sterile for the past five days. All stitches removed, leaving a sound suture line on both the mucous and the skin surfaces. Aug. 5: Discharged to a convalescent home. On Sept. 23 he returned to duty, wearing dentures with comfort and showing negligible scarring.

Case 1318.—An elderly woman giving a history of swelling of the right side of the face, starting early in 1941. Has spent many months in hospitals, and has had extractions of roots, drainage of abscesses, and removal of sequestra. Examination (May 18, 1943) showed a swelling of the whole body of the mandible, with multiple sinuses in the mouth and two discharging wounds under the chin. May 22: The mandible was exposed from the right coronoid notch to a point an inch above the angle on the left side. The lower margin and the outer plate were excised over this area to expose a cavity in the mental region about 2¼ by 1 in. containing a sequestrum which was in fact a circumscribed area of osteitis fibrosa. In the region of the angle and ascending ramus on the right was a similar area of osteitis fibrosa, which was uninfected. In less degree the same condition was present on the left. All abnormal bone, infected or not, was removed, and the wound sutured, except for 1/4 in. at the posterior end on each side. (This was the first case treated with penicillin, and the only one in which tubes were not inserted.)



a

b

FIG. 2.—Case No. 1318. Occlusal radiographs showing: (*a*) an area of osteitis fibrosa lying as a sequestrum in the mandible; (*b*) appearance of the same jaw seven months after excision and penicillin treatment.

A bacteriological swab showed haemolytic streptococci ++, anaerobic *Strep. viridans* ++, and monilia. 4,000 units of penicillin were injected for the first two days, and thereafter 2,000 units a day for the next five days. May 27: Sutured wound healed, though the posterior sinuses were still open but sterile. June 22: Spontaneous discharge of much pus, together with one small sequestrum, evidently overlooked at operation. Cultures sterile. June 29: All wounds, both on the surface and in the mouth, soundly healed. Feb. 19, 1944: Review. There has been no further disturbance. The scars are satisfactory, and the radiograph shows good bone regeneration, with no evidence of either infection or residual osteitis fibrosa. (Fig. 2.)

Complications

1. The deliberate avoidance of drainage does not prevent the continuance of soft-tissue breakdown, and an accumulation of pus may need evacuation. This has so far been found to be sterile, and the resultant sinus closes rapidly.

2. Persistence of discharge, sometimes associated with a change in bacteria, has occurred twice. In each instance it has been due to incomplete removal of affected bone. One case was subsequently reoperated on with success. The other, which acquired a coliform infection about the tenth day, became much more extensive, and has not yet been subjected to further operation.

3. In two cases removal of all infected bone has created a section of mandibular continuity. In one elderly woman no fixation was necessary, and satisfactory union occurred. In the other case the division was close to the condylar neck, and splintage was applied. It is as yet too early to assess the final result, but union seems to be progressing.

4. When the main infection lies on the lingual side of the jaw the detached muscles of the floor of the mouth swing away from the bone, and in these cases closure of the skin alone leaves a large cavity. It may not always be wise to close the whole wound in these circumstances, but rather to pack with penicillin gauze. Although this may result in bacteriological control, there is no reason to expect much increase in the rate of healing.

Summary

It is pointed out that penicillin is unlikely to give bacteriological control in the presence of sequestra or unfavourable surgical conditions. It is therefore no substitute for adequate surgery.

In four cases in which penicillin has been used as a "prophylactic" there is evidence that the infection has been rapidly controlled without any undesirable local effects.

A conception of the dominant role of vascular disaster in the causation of bone infection is advanced, and a technique for treatment of osteomyelitis of the jaw based upon this is described.

The adjuvant effect of penicillin has led to the conversion of the original open method to a closed one, with all the advantages this confers. In the 16 cases so treated elimination of all penicillin-sensitive organisms, satisfactory soft-tissue healing, and good regeneration of the bone have taken place, so that recovery from what has hitherto been an extremely chronic condition has been effected in an average of about 30 days.

I am indebted to the Penicillin Clinical Trials Committee of the M.R.C. for supplies of penicillin used in this series; to Prof. L. P. Garrod for constant supervision of the bacteriological aspect of these cases; to "Bundles for Britain," who provided a generous fund for the maintenance of the laboratory in which the work was carried out; and to all members of the Plastic and Jaw Unit at Hill End Hospital, who have been of so much assistance in the clinical control of the cases. To all of them I desire to express my very sincere thanks.

PENICILLIN IN BONE INFECTIONS

BY

IVOR M. ROBERTSON, F.R.C.S.Ed.

Apart from the observations of Florey and Florey (1943) on the treatment of acute osteomyelitis, there is little published information about the use of penicillin in orthopaedic surgery. An attempt has therefore been made to explore its value further, and the results in 34 cases will be described, nine of which received systemic and the remainder only local treatment.

Acute Haematogenous Osteomyelitis

This group comprised 7 cases, all in children. With one exception penicillin was used as an adjunct to surgery; the wounds following surgical exploration were packed lightly with petroleum jelly gauze and enclosed in plaster, a window being cut to allow of inspection and taking swabs for culture. Systemic penicillin treatment was given by various routes, dosage being calculated roughly according to body weight, and based on an adult dose of 120,000 units daily. The methods of administration used are described by Morgan, Christie, and Roxburgh (p. 515).

Case 1.—K. P.; female, aged 12. Acute osteomyelitis of lower third of right femur of 3 days' duration. Coagulase-positive *Staph. aureus* in blood and pus. Treated by incision of subperiosteal abscess and drilling of femur. Penicillin treatment began on fourth day of disease (1,031,000 units in 13 days). On completion of systemic treatment the wound was packed for the next 24 hours with gauze soaked in penicillin solution. Thereafter, decreasing amounts were instilled into the wound daily. Penicillin cream was employed in later stages of healing. The total amount used for local treatment was 62,000 units. Wound sterile on 14th day; complete epithelization on 32nd day. *X*-ray changes minimal.

Case 2.—J. B.; male, aged 14. Acute osteomyelitis of lower third of right femur of 8 days' duration. Blood culture and pus: coagulase-positive *Staph. aureus*. Treated by incision of subperiosteal abscess and drilling of femur. Penicillin given systemically (860,600 units in 14 days). Effusion into right knee-joint aspirated at same operation (culture, *Staph. aureus*). Joint aspirated on 4 occasions on alternate days and 10,000 units penicillin injected. After 4th aspiration the contents were sterile. Knee recovered full function. Wound sterile on 14th day; completely healed on 43rd day. *X*-ray changes minimal.

Case 3.—P. R.; female, aged 12. Acute osteomyelitis of upper third of right femur of 31 days' duration. Coagulase-positive *Staph. aureus* in pus from wound. Treated by exploration of upper third femur and drainage of large subperiosteal abscess. Penicillin given systemically (1,087,000 units in 20 days). Further exploration 15 days later. Trochanter region of femur opened up by guttering. Wound healed in 100 days. Further exploration became necessary. Gross *x*-ray changes present. Penicillin therapy was restarted; 660,000 units given intramuscularly over period of 11 days. Wound healing.

Case 4.—R. P.; male, aged 12. Acute osteomyelitis of lower third of right ulna, upper third right humerus, lower third of right and left femur of 14 days' duration. Coagulase-positive *Staph. aureus* in blood culture and in pus from superficial abscess. Extremely ill. Temperature 102°; pulse 110. Bronchopneumonia present. Pain and tenderness were not localized to areas indicated above, but were associated with effusion, pain, and stiffness of all neighbouring joints. Superficial abscess discharging on forearm. No indication as to the site of primary focus, and bony lesions were never localized enough to merit surgical incision. Treated by intravenous penicillin; later changed to intramuscular drip. Total amount given, 761,250 units in 10 days. Complete recovery in 60 days. *X*-ray changes minimal.

Case 5.—J. B.; male, aged 10. Acute osteomyelitis of lower third of right femur of 2 days' duration. Coagulase-positive *Staph. aureus* in pus from wound. Treated by incision and drilling. Penicillin given intramuscularly (434,350 units in 9 days). Wound granulating. Temperature normal. On the 6th day after treatment the left leg became tense and painful. There was a rise of temperature, which continued until the intramuscular drip was discontinued. Temperature fell immediately, and has remained normal ever since. Wound epithelized in 45 days. *X*-ray changes minimal.

Case 6.—B. W.; male, aged 5. Acute osteomyelitis of upper third of right tibia of 10 days' duration. Blood culture sterile. Coagulase-positive *Staph. aureus* in pus. Treated (before admission) by sulphathiazole (14 g.). When admitted, treated by incision and drilling. Penicillin given intramuscularly (440,000 units in 11 days). On the 6th day of intramuscular treatment the left leg became tense and painful. This was accompanied by an inguinal adenitis and rise of temperature. On 10th day wound sterile. Secondary suture performed. Small rubber tube inserted through upper end of wound. Penicillin instilled daily for 11 days (36,000 units). Wound soundly healed in 26 days. *X*-ray changes minimal.

Case 7.—D. E.; female, aged 18 months. Acute osteomyelitis of upper third of left tibia of 1 day's duration. Coagulase-positive *Staph. aureus* in pus. Treated (before admission) by sulphathiazole (4 g.). When admitted, treated by incision and drilling. Intramuscular injections of penicillin given 3-hourly (350,000 units in 12 days). Still under treatment.

Comment.—Case 4 differs from the rest in that no surgical treatment was employed. This boy had a positive blood culture and a severe infection which might well have been fatal. A positive blood culture was also obtained in Cases 1 and 2. It is noteworthy that a favourable course follows when treatment is begun early: the best results were in Cases 1, 2, 5, and 6, in which the disease had existed for 3, 8, 2, and 10 days respectively. Case 3, with a pre-treatment duration of 31 days, is the only one in the series to run a prolonged course, and is not yet well.

These results may be compared with those of McKeown (1943), who describes 26 cases treated with sulphathiazole and various types of surgical intervention. The 17 cases treated with sulphathiazole and by bone-drilling at an early stage of

the disease gave the best result of any method used, and reduced the duration of the disease by 60%. Of the 17 cases, none was healed completely under three months. Most of the cases healed in three, four, or five months, but the average was six months. Four cases in our series of six (i.e., excluding Case 4, which did not require surgical intervention) healed completely, with minimal *x*-ray changes, in 32, 43, 45, and 26 days respectively. These four cases have encouraged us in the hope that the duration of the disease may be further curtailed by the use of penicillin.

Local Treatment

(a) Chronic Haematogenous Osteomyelitis

In the local treatment of this condition penicillin was used in three forms: (i) a solution of calcium penicillin in distilled water usually of a strength of 1,000 units per c.cm.; (ii) a cream containing 400 units per gramme in a base consisting of equal parts of lanette wax S.X., petroleum jelly, and water; (iii) powder containing 2,000 units per gramme in sulphanilamide with 5% magnesium oxide added to prevent caking. The position, nature, and extent of the infection had to be taken into account when deciding on choice of preparation and method of application. Cases with sinus formation leading down to infected bone were usually treated with penicillin in solution, instilled either directly into the sinuses or through a small-bore rubber tube or tubes extending well down the sinus. In some cases the tube was withdrawn immediately after each treatment, but in others it was left in place and withdrawn gradually each day. The tubes were kept in position on an average from 7 to 10 days, depending on the bacteria present. Bacteriological examinations were made frequently from the aspirated material.

Cases in which surgical treatment had been limited to sequestrectomy presented a more difficult problem. A bony cavity was usually present, and its position often made retention of penicillin solution extremely difficult if not impossible. In some cases it was possible to maintain a tube in position so that the injected penicillin had some chance of reaching all infected areas. The amount of penicillin injected varied with the size and extent of the bone cavity. From 4 to 10 c.cm. was used on an average. The tube was closed by a spigot to prevent loss, and the instillations were made once every 24 hours.

In many cases closed plasters were used, with a window cut to allow dressing and inspection of the wound. This was restricted as much as possible, the tube being led through the dressings so that the daily injections could be carried out without disturbing the wound itself. Cases with exposed bone, and particularly those presenting a "trough" appearance, were filled with penicillin solution, and retention was maintained by splinting or positioning the limb. In cases that had been "saucerized" penicillin–sulphanilamide powder or cream was used. Applications were made once every 24 hours.

Case 1.—M. H.; female, aged 20. Osteomyelitis of femur of 3 years' duration with wide sinus leading to bone. *Staph. aureus.* Treated by sequestrectomy followed by direct application of solution through tube fixed into sinus. 7,000 units per day for 7 days. Wound sterile after 5 days and healed completely in 3 weeks. (Solution was well retained in this sinus, and fluid withdrawn before a further injection was still active.)

Case 2.—M. J.; female, aged 34. Sinus over right sacro-iliac joint in connexion with old tuberculous joint. Duration, 9 years. *Strep. pyogenes* and *Staph. aureus.* Treated by instilling penicillin solution into the sinus (72,500 units in 13 days). Temporary slight improvement, but relapse after stopping treatment.

Case 3.—W. H.; male, aged 48. Chronic osteomyelitis of femur of 30 years' duration with a large elongated cavity (5 by 1½ in.) on outer aspect of thigh extending to bone. *Strep. pyogenes, Staph. aureus,* diphtheroids, and coliforms. Treated by exploration. No sequestra found. Positional flooding of cavity with penicillin solution (131,000 units over 12 days). No improvement.

Case 4.—J. F.; male, aged 19. Chronic osteomyelitis of lower third femur of 2½ years' duration, with several small sinuses and incompletely healed wound of sequestrectomy. Gram-positive cocci, diphtheroids, and *Proteus.* Treated by sequestrectomy. Sinus injected with penicillin solution through catheter (40,000 units in 34 days). Wound packed with cream. Sinuses persisted.

Case 5.—W. B.; male, aged 33. Chronic osteomyelitis of lumbar vertebra (4), with track leading out above left iliac crest; 8 months' duration. *Strep. pyogenes* and *Staph. aureus.* Treated by dilatation of sinus at operation. Tube left *in situ.* Penicillin solution run in through tube (31,000 units in 9 days). Wound sterile in 3 days. Sinus much smaller.

Case 6.—J. S.; male, aged 41. Acute exacerbation of chronic osteomyelitis of 3 months' duration, with cavity in upper end of tibia (2 by 3/4 in.) leading to sinus. *Staph. aureus.* Treated by drilling bone and scraping cavity. Wound partially closed and tube left in, extending down to bone cavity. Penicillin solution instilled daily (36,600 units in 6 weeks). Sinus healed temporarily.

Case 7.—T. P.; male, aged 19. Chronic osteomyelitis of right tibia of a year's duration, with a large open cavity on the anterior surface containing stinking pus and with sloughs on its soft-tissue walls, exposing bone of upper third, and multiple sinuses. *Staph. aureus* and *Proteus.* Treated by positional flooding with penicillin solution (311,000 units in 41 applications over 3 months). When treatment was begun, amputation of this leg had been advised. The limb being immobilized, the solution was retained in the large cavity although this was wide open, and usually preserved its activity until renewed. The exudate lost its offensive smell; the borders of the cavity became clean, and its size steadily diminished until it had almost completely filled up and healed by granulation. Unfortunately, other sinuses discharged, and further sequestrectomies have since been necessary: the patient is still under treatment.

Case 8.—R. N.; male, aged 18. Sinus of right groin due to chronic osteomyelitis of ilium of 6 years' duration. *Staph aureus.* Treated by instillation of penicillin solution into sinus with catheter *in situ* (32,000 units over 16 days). Discharge sterile on the 12th day. Sinus healed at the end of course of treatment, but later broke down.

(b) Osteomyelitis after Compound Fractures

Five such cases were treated by similar methods, of which brief histories follow together with those of two infected operation wounds.

Case 9.—W. D.; male, aged 30. Small wound on anterior aspect of right leg with bare bone visible, of 6 weeks' duration, the result of a compound fracture of the tibia. *Strep. pyogenes* and *Staph. aureus.* Treated by application of penicillin powder and later cream to the wound (14,300 units in 17 days). Wound was then explored and several small sequestra removed. A rubber drainage-tube was inserted through a separate stab wound and the skin edges closed. Penicillin solution was instilled (136,000 units over 16 days). Tube and stitches were then removed, and the wound, which appeared to be healed, was insufflated with powder. Wound broke down slightly two days later, and was treated with a further 23,000 units of solution. This sinus healed in 15 days and remained healed for two months, when it broke down again.

Case 10.—F. S.; male, aged 42. Long scar on anterior aspect of leg with granulating gutter leading to necrotic bone at lower end, due to chronic osteomyelitis of 19 months' duration, following compound fracture of the ankle. *Staph. aureus* and diphtheroids. Treated by insufflation of penicillin powder (30,000 units in 25 days). Infection persisted.

Case 11.—R. H.; male, aged 21. Gutter-shaped wound of 13½ weeks' duration, 7 in. long, on antero-lateral surface of leg, with bone exposed at lower end, due to compound fracture of tibia. *Staph. aureus* and *Proteus.* Treated by positional flooding with penicillin solution (14,000 units in 2 days). After sinuses had been laid open at operation, powder was used (36,000 units in 18 days). No change in the condition of the wound. Infection persisted.

Case 12 (a).—W. S.; male, aged 36. Cross leg flap to repair skin loss of right leg due to chronic osteomyelitis of 2 years' duration. *Strep. pyogenes* and *Staph. aureus.* Treated by injection of penicillin solution (two doses) into wound and by application of cream (27,000 units in 15 days). Wound rendered sterile.

Case 12 (b).—Further course of treatment undertaken 3 weeks later. *Strep. pyogenes* (Type 27) and staphylococci. Treated by injection of penicillin solution below flap (42,000 units in 2 weeks). Osteitis remained unchanged.

Case 13.—F. L.; male, aged 40. Infection, of 6 weeks' duration, of iliac crest, which was donor site for cancellous bone graft. *Strep. pyogenes* and *Staph. aureus.* Treated by injection of penicillin solution into infected wound (18,000 units in 9 days). Streptococci disappeared in 24 hours. No clinical improvement.

Case 14.—J. G.; male, aged 26. Active sinus of 3 months' duration leading to chronic osteomyelitis of lower third tibia of 2 years' duration following compound fracture. *Staph. aureus.* Treated by introduction of penicillin solution into sinus (24,000 units over 12 days). Sinus closed, but later broke down.

Case 15.—R. T.; male, aged 48. Widely infected wound (7 by 3 in.) of 3 weeks' duration, following bone graft at lower end of tibia. Graft exposed. *Staph. aureus* and *Ps. pyocyanea.* Treated by applying penicillin solution with a spray (32,000 units in 9 days). Infection persisted.

Comment.—The results of treatment by local application of penicillin in cases of chronic bone sepsis have so far proved very disappointing. Of these 16 cases complete healing occurred

in one only. In seven there was only temporary improvement, and in eight none. At least three factors appear to be responsible for the unsatisfactory results:

1. *Failure of Continuous Application.*—The mechanical difficulties of securing continuous action are great. Solution may escape from sinuses and often cannot be retained at all in large shallow wounds. Case 7 was an exception: complete immobilization enabled a lake of solution to be maintained in the wound for two months, which steadily proceeded to heal in spite of the presence of a resistant organism (*Proteus*) together with a susceptible one (*Staph. aureus*).

2. *Inaccessibility of the Bone Infection.*—In many cases it seemed improbable that the penicillin solution instilled down a sinus or introduced into a bone cavity reached the whole of the infected area —areas of deep osteitis persisting, and only the superficial infection being affected (e.g., Cases 4, 6, and 7). It was shown in Case 9 that a bone cavity can be sterilized temporarily, but on the cessation of treatment the infection recurred. Re-infections may occur from the skin in some instances, but in a number of cases it was observed that the infecting organism was identical with that present in the wound before sterilization (Case 12, *a* and *b*). This suggests that the deeper areas of osteitis remained untouched.

3. *The Presence of Dead Bone.*—Regardless of their accessibility or otherwise to penicillin, however administered, there were evidently, in some of these cases, areas of bone of which the surgical removal was necessary before healing could occur. In the presence of sequestra, penicillin treatment unaided by surgery has been unsuccessful.

In the group of compound fractures, those cases presenting a guttered wound with gross skin loss and bare bone exposed in the depths were particularly resistant to treatment, the mixed bacterial flora remaining unaltered and the healing of the wound being delayed (Cases 10, 11, and 15).

It is hoped to improve on these discouraging results by a policy that is now under trial in several cases, results of which are not yet available. This is the more radical removal of infected bone, followed by complete closure, if necessary with the aid of a full-thickness graft, and subsequent instillation of penicillin solution through a tube.

Miscellaneous Cases

In this group 12 miscellaneous orthopaedic cases were treated with penicillin—ten locally and two systemically.

Section 1—Local

(*a*) Post-operative wound infections (5 cases). (*b*) Soft-tissue sinus associated with chronic osteomyelitis of hip (1 case). (*c*) Infected Steinmann-pin holes (2 cases). (*d*) Gunshot wound of shoulder region (1 case). (*e*) Chronic sinus associated with plating of femur (1 case).

(*a*) Five cases of post-operative wound infections were treated at intervals varying from 3 to 130 days after operation. In all cases the method was to instil the solution by means of a catheter into the sinus twice daily, the total dose varying with the size of the sinus and the duration of the treatment. The average was 39,000 units in 3½ days. Two cases healed completely, two showed temporary improvement, and one showed no improvement.

(*c*) Two cases of infected Steinmann-pin holes were treated. The pin tracks were in the upper end of the tibia just below the tubercle. They were treated by injection of penicillin solution into the track. Complete healing occurred in both cases at the end of 27 and 13 days respectively.

(*d*) A case of osteomyelitis of left shoulder with chronic sinus resulting from a gunshot wound of the shoulder 10½ months previously, and with a foreign body still in the depths of the wound. This case was treated by surgical drainage and the instillation of penicillin solution by means of rubber catheters into sinuses daily for 25 days (total, 235,500 units). This resulted in a slight improvement in the condition of the wound.

(*e*) A case of infection in a plated femur treated by local applications of penicillin solution unsuccessfully. The plate was later removed at an operation, and a subsequent course of penicillin therapy was carried out (101,000 units in 13 days, introduced into a catheter fixed *in situ*). Complete healing occurred in 19 days.

Section 2—Systemic: Compound Fractures associated with Chronic Osteomyelitis

Case 1.—J. P.; male, aged 38. Deep epithelized trough of 6 months' duration on anterior surface of lower leg with an island of bare bone in centre following compound comminuted fracture of upper end of tibia with gross skin loss. *Staph. aureus;* diphtheroids. *Systemic treatment:*—Intravenous penicillin, 30,000 units per pint of dextrose-saline 6-hourly for 6 days (total, 720,000 units). Discontinued owing to thrombophlebitis of long saphenous vein. Intramuscular injections (15,000 units 3-hourly for 4 days; total, 480,000 units). Injections discontinued owing to patient's complaining of severe cramping pains at site of injection. Intravenous penicillin restarted, and given for 3 days (total, 360,000 units). *Local treatment:*—3,500 units of penicillin cream applied to wound daily for 3 days. Systemic treatment had been discontinued. *Result:*—The wound was sterile at the end of the course of treatment and permitted delayed secondary suture of the wound with excision of protruding necrotic bone. Wound remained healed for seven weeks and then broke down. The infecting organisms were identical with those present before sterilization.

Case 2.—F. S.; male, aged 42. Trough-shaped discharging wound (2½ by 1 in.) with bare bone visible at the lower end of tibia of 18 months' duration, following compound fracture-dislocation of ankle. Coagulase-positive *Staph. aureus* and diphtheroids. *Systemic treatment:*—Intravenous penicillin was given, 30,000 units per pint of dextrose-saline 6-hourly for 5 days in left leg (total, 600,000 units). This was discontinued owing to increasing oedema of left leg due to thrombophlebitis. Intramuscular injections (15,000 units 3-hourly for 6 days; total, 720,000 units). This was accompanied by a persistent pyrexia (100–102°) throughout course of systemic treatment. *Local treatment:*—13,000 units of penicillin were applied over a further 25 days in the form of cream. *Result:*—Staphylococci and streptococci had disappeared by the 11th day of systemic treatment, but coliforms persisted throughout. Considerable improvement in the wound permitted further sequestrectomy. Healing has progressed slowly, but no major breakdown of the wound has occurred since.

Comment.—The majority of the locally treated cases in this miscellaneous group responded well, possibly because the lesions were of small extent, involving mainly soft tissues, and usually not of long standing. The two cases treated systemically were costly failures: over a million units of penicillin were used in each with little ultimate benefit. This drastic treatment was decided on as an experiment when local application in similar cases had failed. To judge by its results in these two cases, this expenditure of penicillin is unjustified, and long-standing sepsis involving bone must be considered an unfavourable field for treatment, either local or systemic.

Summary

Early acute haematogenous osteomyelitis was treated systemically with penicillin in 7 cases with good results; 6 of these were also subjected to orthodox surgical treatment.

Systemic treatment in 2 cases of chronic sepsis following compound fracture was of only temporary benefit.

Local application of penicillin was employed in treating 8 cases of chronic haematogenous osteomyelitis, 7 cases of osteomyelitis following compound fractures, and 10 miscellaneous cases, mainly chronic sinuses. The reasons for the failure of the treatment in many of these cases are discussed.

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THE LOCAL APPLICATION OF PENICILLIN IN SOFT-TISSUE LESIONS

BY

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AND

O. T. MANSFIELD, F.R.C.S.

This report deals with cases under treatment in an E.M.S. plastic unit. The surgical treatment of these cases involved reconstructive procedures for various types of tissue loss, under conditions in which the control of infection by pyogenic organisms has always been a predominant problem. The cases reported do not represent the total number treated (45 out of 70), but are chosen only on the grounds that reasonable conclusions can be drawn from them. Of these selected cases seven are detailed in the text as illustrations. Because of the wide variety of conditions treated, a somewhat arbitrary classification is adopted in order to avoid innumerable subdivisions. These can in no way be considered as a series.

Group A: Infected Skin Lesions

These consist of infected eczemata, impetigo, the so-called capillary lymphangitis, and similar skin eruptions with pustule

formation. Several have occurred on Thiersch graft donor areas. There were 7 cases in this group, all infected with haemolytic streptococci, staphylococci, or both. All except one cleared up in 10 to 14 days, but some relapsed later. In all cases the preparation used was a cream containing 400 units of penicillin per gramme in a base composed of equal parts of lanette wax S.X., soft paraffin, and water.

Case 1.—A soldier aged 29 had a surgical correction of an adherent scar on the dorsum of the right index finger. After operation he developed a staphylococcal eczema round the surgical area, and the infection involved the suture lines. This was sterilized in two days with penicillin and remained sterile for eight days, in spite of which the eruption spread.

The occurrence of an eczema induced by the use of the cream in two subsequent cases provides a possible explanation of this result. One of these later cases had a positive patch test to the cream, the presumed irritative agent being the soft paraffin employed. This is under investigation.

This group of cases suggests that skin lesions infected with penicillin-sensitive organisms respond according to the technique of application. Where the lesions were open and the penicillin had ready access to the foci of infection the results were satisfactory, but in closed lesions temporary improvement was followed by relapse when treatment was stopped. It is possible that careful skin toilet followed by penicillin inunction may prove to be more effective in these resistant cases.

Group B: Abscess Cavities

Penicillin solution in a strength of 1,000 units per c.cm. was injected into five abscess cavities. Of the results two were successful, one was doubtful, and there were two failures.

Case 2.—A woman aged 22 for whom a cancellous iliac bone graft was used to reconstruct a syphilitic saddle deformity of the nasal bridge. After operation she developed a haematoma in the region of the graft in the nasal bridge. This remained quiescent for seven days and then suddenly became infected. She was returned to the theatre and bilateral drainage instituted. There was a mixed haemolytic streptococcal and staphylococcal infection, which responded immediately to penicillin injected into the cavity, and the drainage wounds were healed in four days. There was no loss of the cancellous bone.

Case 3.—A man aged 22 for whom a bone graft similar to that described above was used in the correction of a traumatic nasal bridge deformity. There was a rapid post-operative infection, with pus formation on the third day. At this time bilateral drainage was done and penicillin injection started. The infection was penicillin-sensitive *Staph. aureus*. This treatment was continued for a week with no change in the discharge or the infection, so that penicillin was discontinued. Conservative treatment was advised, and the discharge gradually decreased until a month later a small sequestrum was evident, the removal of which effected rapid healing.

Consideration of these two cases shows that one salient feature was the time of onset of the infection. Advocates of the cancellous-bone-grafting technique hold that this bone derives a primary blood supply from the surrounding tissues and thus survives as a true graft. In Case 2, then, several days had elapsed before infection supervened, so that the bone cells by that time might be considered to have survived the transplanting procedure. Under these conditions the early treatment of infection should tend to prevent sequestration and thus promote the rapid resolution of the infective process.

In Case 3 the disaster occurred before viability was established in the graft, so that in spite of treatment a portion of the bone died and thus perpetuated the infection, which did not clear up until sequestration was complete. The small size of the sequestrum (it was a wafer from the subcutaneous surface of the bone) does suggest that this tissue lends itself favourably to transplantation.

A further inference that can be drawn is that penicillin in the presence of necrotic tissue does not appear to have much influence upon the infection. In this and other similar cases no clinical improvement was demonstrated with the use of penicillin. Thus where a penicillin-sensitive infection does not rapidly respond to adequate application much time will be saved if a search for complicating factors is made.

Case 4.—A young soldier was admitted for reconstruction of the chin and incisor region of the mandible, lost as the result of a gunshot injury. The mandible had been made good by a bone graft, and at the stage under discussion his lower buccal sulcus had been re-made by a Thiersch grafting operation. Owing to a small breakdown in the graft an abscess appeared in the soft tissues of the chin. The bacteriology was very mixed, some organisms being sensitive to penicillin and others not. The treatment consisted in filling the cavity via the mouth with penicillin after expression of the pus. Although a small fistula opened on to the skin surface, the abscess was healed in six days.

This type of breakdown has in the past been a matter for regret, in so far as many weeks pass before it attempts to heal and considerable scar is left in its train. In the above case it is felt that the early control of infection in this area prevented sufficient breakdown for the wound to become chronic.

The case in this group which has been described as doubtful was a surgically drained subcutaneous abscess in a hand, the organism being a penicillin-sensitive staphylococcus. This case followed the ordinary course resulting from adequate surgical drainage, and did not present any special features during the healing phase.

Case 5.—This patient was an 11-year-old boy with a severe phosphorus burn of the leg of three months' duration. The soft tissues on the posterior aspect of the knee-joint had been destroyed, leaving the external femoral condyle visible in the wound. He was critically ill at this stage with an intermittent profuse purulent discharge from an acute pyarthrosis, and an endeavour was made to combat this infection by the local instillation of penicillin into the joint cavity by means of Carrel tubing. This treatment resulted in no improvement, and it was quite obvious that the penicillin did not have access to all parts of the infected joint. The treatment was stopped and traction applied. Slow improvement occurred, until eventually the joint sinus healed.

This case illustrates well the precept that the technique of application must be efficient or the results will be unfavourable. The results of local application are truly local, so that adequate access must be provided.

Group C: Acute Spreading Cellulitis

Five cases of acute invasive infection under skin flaps designed for reconstructive purposes were treated by the early instillation of penicillin solution. In all cases progress of the infection was halted and resolution was rapid. Previous experience of this complication with skin flaps, the blood supply of which is necessarily much curtailed, confirms that these results have not been attained by other methods of treatment.

In the second series of cases under this heading 11 insets of tubed pedicle grafts were treated in a similar manner. In five of these loss of tissue resulted which necessitated further surgery; in the other six the insets survived. The controlling factor appeared to be the blood supply of the part rather than the infection. In some of these cases, although the infection was controlled, retrograde intravascular thrombosis continued, with progressive tissue loss.

From the results in this group it is felt that penicillin is of value in controlling infection which the depleted blood supply of the tissue itself would be unable to cope with, and on these grounds the prophylactic use of penicillin may have a wide application.

Group D: Superficial Wounds with Skin Loss

In this category there were 17 cases. All were treated with penicillin cream. The variety of these lesions introduces so many extraneous factors that general conclusions are all that can be drawn from them. These conclusions can be illustrated by individual case reports.

(*a*) Penicillin can sterilize a wound and prevent its reinfection with sensitive organisms. It does not necessarily follow that a wound thus sterilized will heal.

Case 6.—A soldier aged 23 was given *x*-ray therapy three years previously for warts on the right hand. He was admitted for the treatment of a radio-necrosis of the index finger and thumb, the middle finger having already been amputated. During a skin-flap replacement of the dorsum of the index a linear breakdown occurred in a suture line, which became infected with *Staph. aureus*. This was sterilized in two days and kept sterile for 32 days by using penicillin cream. During this time there was no attempt at healing, and a cervical sympathetic block was done. This produced a response in the disorganized vascular system and the wound healed.

(*b*) If reinfection of a wound occurs after sterilization by penicillin a sensitivity test should be done on the new invader, as it may be resistant.

Case 7.—A soldier aged 23 was undergoing total reconstruction of the thumb. A pedicle graft had been raised and transferred to the thenar remnant, and at this stage both ends of the pedicle were attached to the hand. As the result of some slight trauma the pedicle ulcerated and became infected with penicillin-sensitive *Staph. aureus*. Penicillin cream was used as a dressing, and sterility was obtained in five days. The wound remained sterile for 16 days without any clinical change and then became reinfected with staphylococci. Penicillin was continued for 27 days without clinical or bacteriological effect. Finally treatment was stopped and the ulcer eventually healed.

(*c*) Although sensitive organisms may disappear from culture, the wound may be so infected with *pyocyaneus, proteus,* or the coliforms as secondary invaders that no clinical improvement is noted or indeed can be expected. This was a common finding, particularly in this group of cases.

(*d*) Penicillin can be a useful adjunct to surgery, but does not replace it. Certain surgical principles may need modification to comply with the requirements of penicillin application.

Summary

These experiments with the local use of penicillin to date indicate that we have an effective weapon in the fight against tissue invasion by certain of the pyogenic cocci. The points that emerge are:

1. Early application is most desirable.

2. Efficient technique must be used to bring penicillin into contact with the infective process.

3. Tissues necrosed as the result of infection are removed by natural processes. Many wounds containing slough or sequestra resist sterilization by penicillin. In some of these cases it is probable that attempts at sterilization impede slough removal and so delay healing.

4. Penicillin as an adjunct to adequate surgical technique is a valuable advance in the treatment of wounds infected with sensitive organisms.

LOCAL TREATMENT OF BREAST ABSCESS WITH PENICILLIN

BY

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Simple aspiration under local anaesthesia has in some hands given good results in the treatment of mammary abscesses, and it seemed logical to add to this penicillin replacement when supplies became available. A series of 15 consecutive cases has been treated, and case histories, with interpretation of results, are here given.

The technique used was simply to infiltrate the skin with a stab of 2% novocain and to aspirate through a needle with a 20-c.cm. syringe. Staphylococcal pus is sometimes thick and breast abscesses are notoriously loculated, but by using saline wash-outs when necessary it was usually possible to evacuate them with fair efficiency. The organism in every case proved to be coagulase-positive *Staphylococcus aureus.* No strains resistant to penicillin were encountered. A solution of calcium penicillin in distilled water of a strength of 2,000 units per c.cm. was then injected through the same needle, dosage varying from 2,000 to 20,000 units according to the size of the abscess. Aspiration and injection of penicillin were usually repeated at two-day intervals: the pus obtained on the second and subsequent occasions was usually sterile or nearly so, and, when placed in an agar cup in a plate inoculated with the standard Oxford H staphylococcus, produced a zone of inhibition indicating that penicillin was still present in effective concentration after 48 hours. I am indebted for the bacteriological investigations to Dr. J. C. Ford.

Except in three of the earlier cases, breast-feeding was discontinued and lactation suppressed by restriction of fluids, mild aperients, and stilboestrol 5 mg. daily for 5 days. The breasts were firmly supported with crêpe elastic bandages.

Case Histories

Case 1.—Primipara aged 23. Painful breast after 5 weeks of lactation. Admitted Jan. 15, 1944, with large breast abscess and infection involving most of breast. Same day: Aspiration 40 c.cm. pus; 12,000 units penicillin. Jan. 16: Aspiration 16 c.cm. pus; 10,000 units penicillin. *Result:*—Next day spontaneous discharge from aspiration site and rapid resolution. Home in 8 days.

Case 2.—Multipara aged 30. No recent pregnancies. Two small breast abscesses in past year treated by surgical drainage. Three weeks ago, gradual development of another, involving one-third of the breast above and behind areola. Dec. 28, 1943: Aspiration 7 c.cm. pus; 10,000 units penicillin. Dec. 30: Aspiration 12 c.cm. pus; 8,000 units penicillin. Jan. 1, 1944: Aspiration 14 c.cm. pus. *Result:*—Remained closed, and on Jan. 14 there was good resolution.

Case 3.—Aged 23. Breast abscess following weaning at 10 months, involving about one-quarter of breast. Duration 8 days. *Treatment:*—July 11, 1943: 10,000 units of penicillin injected immediately after aspiration of 5 c.cm. of pus; pentothal anaesthesia, as patient was very nervous. Twenty-four hours later, second aspiration: no anaesthesia: 5 c.cm. of sterile pus which inhibited growth of staphylococci to a distance of 4.5 mm. 5,000 units again injected. *Result:*—Abscess pointed 2 days after starting treatment. Discharged profusely and healed rapidly. Patient was afebrile in 3 days; home in 6 days.

Case 4.—Aged 25. Breast abscess following lactation. Child 3½ weeks old. Breast had been uncomfortable for 2 weeks and a lump had gradually appeared. Four days before admission the lump looked yellow, and the whole breast was painful. Two days later the abscess burst; the pain got worse, and on admission was radiating to the axilla and the arm. *Treatment:*—Aug. 10, 1943: 6 c.cm. of pus aspirated from the abscess and 10,000 units of penicillin injected. Aug. 12: 8 c.cm. of pus aspirated and 10,000 units of penicillin injected. 9 mm. inhibition. Aug. 13: Under local anaesthesia incision of abscess and drainage of 10 c.cm. of pus. This pus produced an 8-mm. zone of inhibition, and on a blood-agar plate grew only 8 colonies of *Staph. aureus.* Aug. 27: Breast-feeding discontinued. Aug. 31: Under general anaesthesia—incision and drainage of a large retromammary abscess. The pus from this gave a profuse growth of *Staph. aureus* on blood agar, and failed to produce any zone of inhibition. Sept. 12: Wound healing well. Sept. 14: Breast healed; patient discharged. *Result:*—The patient was febrile until the retromammary abscess was drained on Aug. 31, after 23 days in hospital, and was discharged after 37 days in hospital. Local treatment and the effort to maintain breast-feeding were a failure.

Case 5.—Aged 19. Breast abscess after ceasing to feed baby 6 weeks old. Lump in breast noticed for 3 weeks; increased recently. Abscess involving about one-quarter of breast. *Treatment:*—July 11, 1943: Under local anaesthesia 3 c.cm. of pus aspirated and 4,000 units of penicillin injected. Forty-eight hours later, 3 c.cm. of pus aspirated, which was sterile and gave a 1-mm. zone of inhibition. 6,000 units again injected. *Result:*—Three days after onset of treatment abscess pointed and discharged. Patient was afebrile on third day and home on sixth.

Case 6.—Aged 22. Breast abscess following lactation. Child 5 months old. Eight days before admission lump appeared in right breast. Disappeared after three days. Three days before admission lump reappeared and became painful. Treated as an out-patient with kaolin poultices. On admission she had a breast abscess 2½ in. in diameter above the right nipple. *Treatment:*—Nov. 10, 1943: Aspiration of 10 c.cm. pus; 10,000 units penicillin injected. Nov. 12: Aspiration of 10 c.cm. pus (this pus inhibited standard staphylococci to 11 mm.); 8,000 units injected. Nov. 14: Aspiration of 10 c.cm. pus; 7,000 units injected. Nov. 16: Aspiration of 7 c.cm. pus (this pus inhibited standard staphylococci to 6 mm.); 10,000 units injected. Nov. 18: Aspiration of 4 c.cm. pus. Nov. 20: Cured. *Result:*—The patient was 9 days in hospital, and afebrile on the third day after starting treatment.

Case 7.—Blind primipara aged 27. Had staphylococcal paronychia at delivery, Sept. 25, 1943. Early in puerperium marked breast engorgement, which went on rapidly to development of bilateral breast abscesses involving most of both breasts. Oct. 14: Aspiration, and penicillin replacement under pentothal. 60 c.cm. pus right —15 c.cm. pus left; 15,000 units of penicillin to each side. Oct. 16: Right, 15 c.cm. pus; 16,000 units of penicillin. Left, 4 c.cm. pus; 8,000 units. Oct. 18: Right, 50 c.cm. pus; 8,000 units. Left, 30 c.cm. pus; 6,000 units. Both breasts then broke down and freely drained through a small hole at the site of aspiration. The right rapidly resolved, and cleared up entirely. She was allowed home on Nov. 14 with sinus discharging in left breast. This had not cleared up by Dec. 24, so she was readmitted and the sinus opened up under anaesthesia, with removal of sloughs. *Result:*—On Jan. 20, 1944, after three months, the right breast texture was normal, the left still slightly indurated.

Case 8.—Para 5 aged 39. Had had breast abscesses after third and fourth children; also small areolar abscess in this pregnancy. Always same breast affected. On tenth day of puerperium admitted with segmental mastitis. 3 c.cm. of penicillin injected under local anaesthesia into affected area. Increased tension caused consider-

able pain, but breast improved for a few days, only to develop a large abscess, which was incised on Nov. 28, with removal of 80 c.cm. of pus; 8,000 units were left in drainage wound. Abscess loculated, and required counter-drainage on Dec. 2, after which she made good recovery. Home after 23 days in hospital.

The patient should not have been encouraged to feed from a breast deformed by past infection and incisions. Prophylactic penicillin found impracticable, and useless locally. Incision was resorted to in order to secure efficient drainage of a deep-seated abscess.

Case 9.—Aged 23. Breast abscess after lactation. Child 3 weeks old. Breast-feeding stopped, as supply insufficient. Patient admitted with abscess involving two-thirds of breast that had been developing over a period of three weeks. A small superficial abscess had been treated by surgical drainage a fortnight before. Considerable induration of the deeper tissues of the breast was noticed at the time. *Treatment:*—On July 17, 1943, the patient came under our care. On the 18th 5 c.cm. of pus was aspirated under local anaesthesia and 15,000 units of penicillin were injected. Twenty-four hours later there was free spontaneous drainage at site of the old incision—pus inhibiting standard staphylococcus to 3 mm. Twenty-four hours later 6,000 units injected, and three days later 8,000 units into indurated area. *Result:*—The patient was 10 days in hospital—afebrile after 7 days.

Case 10.—Aged 29. Breast abscess complicating scabies, which she had had for some weeks. Induration developed in the breast about a week previously. When seen she had an intramammary abscess involving two-thirds of the breast. *Treatment:*—20 c.cm. of pus aspirated under local anaesthetic and 15,000 units of penicillin replaced. Forty-eight hours later 4 c.cm. of pus aspirated with difficulty; this inhibited a growth of staphylococci 11.5 mm. 15,000 units replaced. Forty-eight hours after second injection abscess further localized and pointing on the surface. Incision and drainage done under pentothal; 4 to 5 oz. of pus evacuated. This pus inhibited standard staphylococcus to 5 mm. There was rapid resolution after efficient drainage. *Result:*—Patient was afebrile 7 days from onset of treatment and returned home in 12 days.

Case 11.—Aged 35. Seen in post-natal clinic at 10 weeks, with slight induration in right areola. One week later (Oct. 18, 1943) there was a small superficial abscess: 1 c.cm. of pus aspirated; 4,000 units of penicillin injected. Oct. 20: 1 c.cm. of pus aspirated; 3,000 units injected. Breast-feeding continued. The breast settled down, and she was allowed home on Oct. 22. She returned on Oct. 26 with mastitis involving whole breast which developed overnight. Breast-feeding abandoned. The abscess was incised and drained on Oct. 28; no penicillin was used. The breast slowly resolved, the patient being very ill for a fortnight, and, as a sinus persisted, penicillin was injected down it. On Nov. 22 and 23, 8,000 units; on Nov. 25, 2,000 units were given, but no improvement was noticed, and on the 26th the sinus was explored under general anaesthesia and a slough 2½ by 1½ in. removed. The wound was drained, and 8,000 units of penicillin injected down the tube. The breast rapidly resolved, and was healed by Dec. 1.

In this case an attempt to maintain breast-feeding in presence of breast abscess was a failure: the inefficiency of local aspiration treatment if there is a slough in the depth of the abscess is also illustrated.

Case 12.—Aged 22. Breast abscess following lactation. Child 7 weeks old. Eight days before admission painless lump in left breast. Three days later lump became painful and red, and was treated with kaolin poultices and hot bathing. On admission she had a fluctuating breast abscess 3 by 2½ in. on the outer aspect of the left breast. Nov. 12, 1943: Under local anaesthesia 9 c.cm. of pus aspirated and 10,000 units of penicillin injected. Nov. 14: Several discharging sinuses on under surface of abscess; induration less; 6,000 units injected at site of original injection. Nov. 20: Sinuses beginning to heal; no discharge or induration. *Result:*—The patient was 7 days in hospital, and afebrile the day after the first injection of penicillin.

Case 13.—Aged 35. Developed a segmental mastitis when her baby was 8 weeks old. Baby kept at breast and condition resolved with local treatment, to recur one week later with development of small peripheral abscess. Nov. 14, 1943: Aspiration 1 c.cm. pus; 4,000 units penicillin injected. Nov. 16: Aspiration 1 c.cm. pus; 4,000 units injected. Nov. 18: Aspiration *nil*; 4,000 units injected. *Result:*—The abscess discharged spontaneously; patient returned home on Nov. 23 with breast healed and lactation still well established.

Case 14.—Aged 30. Breast abscess following weaning at 9 months; case first seen with segmental mastitis on Oct. 27, 1943. Stilboestrol and local heat given. Six days later afebrile, but local abscess: 10 c.cm. of pus aspirated; 20,000 units of penicillin injected. Nov. 7: Admitted for aspiration–replacement treatment; doses were 20,000, 8,000, 8,000, and 8,000 units, given on Nov. 7, 9, 11, and 13 respectively. *Result:*—Condition underwent slow resolution without breaking down. There was still slight induration on Nov. 20.

Case 15.—Para-7 aged 45, first admitted on fourteenth day of puerperium with mastitis, which resolved with local treatment and abandoning of breast-feeding. Patient went home after 7 days, to return with abscess. Jan. 13, 1944: Aspiration 3 c.cm. pus; 4,000 units penicillin. Jan. 15: Aspiration 5 c.cm. pus; 4,000 units. *Result:*—Spontaneous discharge from aspiration site, with satisfactory resolution.

Comment

These cases fall into three groups. In 5 cases surgical drainage was necessary, and conservative treatment may be said to have failed. In 7 cases spontaneous drainage occurred, either at a puncture site or elsewhere, and in only 3 did the abscess remain closed and resolve slowly with no evacuation of its contents except by aspiration. On the other hand, the cases in both the second and third groups required no operation or anaesthetic, and their recovery was on the whole more rapid than is usual with simple drainage.

It is possible that some other method of local treatment may give better results, and, in view of the fact that aspiration sometimes cannot sufficiently evacuate the contents of the abscess, surgical drainage followed by instillation of penicillin solution through an indwelling catheter is being used in a further series. When larger supplies of penicillin become available a trial should be made of systemic treatment at an earlier stage in order to control the inflammatory process before suppuration has occurred, and so permit the continuation of breast-feeding.

PENICILLIN IN TREATMENT OF CERTAIN DISEASES OF THE SKIN

BY

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The unique properties of penicillin as an antiseptic suggested that it might be of value in the treatment of some diseases of the skin. This seemed a suitable field of inquiry for two further reasons: first, the probability, from bacteriological principles, of a good response from some of the pyogenic infections of the skin; and, secondly, the likelihood of comparatively small amounts of penicillin being required.

The present survey comprises 75 cases. These were all in-patients, and it was thus possible closely to supervise the treatment, which was by local application alone. All cases were investigated bacteriologically before treatment was begun, and the penicillin-sensitivity of the organisms present was qualitatively determined. Unless otherwise stated, the bacterial flora described as being present was, to a greater or lesser degree, penicillin-sensitive. The number of units used in each case should be regarded as only approximate, and was often related to the extent of the disease rather than to its severity. The word "cure" is used in this paper to imply complete healing of lesions at some particular time. It does not necessarily mean a permanent eradication of the disease.

Sycosis Barbae (15 Cases)

This was chosen as a suitable disease for preliminary investigation because it so often fails to respond adequately to other methods of therapy. Crusts, if present, were removed before penicillin was applied, and shaving was discouraged, especially in the early stages of treatment. Penicillin was usually applied as an ointment containing 400 units of calcium or sodium penicillin per gramme of base, the latter being a mixture of equal parts of lanette wax S.X., petroleum jelly, and water. In a few cases the strength used was 200 units per g., and in some the base contained 50% of water with 25% of each of the other ingredients. It was felt that if the base contained 50% of water it might be of more suitable consistency, but this did not prove to be so. In other cases solutions of penicillin were used.

Case 1.—M., aged 31. Duration of disease 11 years. *X* rays, vaccines, sulphonamides, quinoline, and other local applications had produced only temporary improvement. Numerous small pustules over whole beard area. Organisms, *Staph. aureus*. 12,800 units (calcium salt in lanette base, 200 units per g.) in 16 days. Daily applications to worse side (left) only. Right side similarly treated with lanette base without penicillin. Result was apparent cure on left, very slight improvement on right. Followed by 16,800 units to both sides in 18 days, with apparent cure. A few pustules reappeared 2 weeks later. Three weeks after end of treatment he was sent a further 12,000 units, which he applied during the ensuing 5 weeks. This produced complete cure, which has now lasted 22 weeks.

Case 2.—M., aged 46. Duration 6 years. Temporary improvement only with *x* rays, vaccines, sulphonamides, quinoline, and brilliant green. Extensive crusting of whole beard area and neck and eyebrows. Organisms, *Staph. aureus*. 17,000 units (calcium salt in lanette base (50% water), 200 units per g.) in 17 days. Daily applications to worse side only (left). Base only to right side. Marked improvement on left side; rather less marked improvement on right. Then 9,000 units to both sides in 7 days. Both sides cured. A very mild relapse occurred 5 weeks later. This was not treated. Sixteen weeks after treatment ended he was seen to have a very few small spots, but rather a severe blepharitis. This was cured by the application of 12,000 units in 2 weeks; but by then a few pustules had appeared on the face. These were cured by a further 12,000 units, and the cure has now lasted 9 weeks.

Case 3.—M., aged 49. Duration 7 years. Temporary improvement only with *x* rays, sulphonamides, and numerous local applications. Slight crusting. Organisms, *Staph. aureus*. 4,100 units (calcium salt in lanette base (50% water), 200 units per g.) in 20 days. Daily application to worse side only (left). Result: great improvement on left side. Then 5,600 units to both sides in 14 days. Both sides cured. Slight relapse 10 days later. Five weeks after stopping treatment he was given a further 12,000 units, and responded well. Now cured for 14 weeks.

Case 4.—M., aged 41. Duration 2 years. Temporary improvement only with *x* rays, quinoline, and other local applications. Lesions most prominent on cheeks and upper lip. Organisms, *Staph. aureus* and *Strep. pyogenes*. 8,000 units (calcium salt in lanette base (50% water), 400 units per g.) in 8 days. Daily applications to left side only. Great improvement. Then 34,000 units to both sides in 17 days. Both sides cured. No relapse after 19 weeks.

Case 5.—M., aged 29. Duration 3 years. Temporary improvement only with *x* rays, sulphonamides, and other local applications. Infection confined to upper lip and eyelids. Organisms, *Staph. aureus*. 4,600 units in 23 days. Calcium salt in lanette base, 200 units per g., applied daily to upper lip. Solution of calcium salt (500 units per c.cm.) as eye drops (2 drops into each eye 2-hourly by day) and ointment applied to lids at night, for 5 days. Blepharitis cured, upper lip almost so. Used a further 3,000 units during next 2½ weeks, and was then seen to be cured. Slight return of crusting on the upper lip 15 weeks later. When this had been present one week he was given quinoline emulsion for the next week, and during the subsequent 2 weeks used a further 12,000 units of penicillin. He was then seen to have relapsed almost completely, with some return of the blepharitis. Ointment appeared to be irritating the lesion.

Case 6.—M., aged 22. Duration 4 months. Temporary improvement with *x* rays, ultra-violet light, sulphonamides, brilliant green, crystal violet, etc. Scattered lesions over whole beard area. Organisms, *Staph. aureus*. 7,500 units (sodium salt in lanette base, 400 units per g.) in 30 days. Applications daily for 11 days, then twice daily. Complete cure: has now lasted 16 weeks.

Case 7.—M., aged 22. Duration 3 years. Temporary improvement only with local applications and *x* rays. Lesions extensive; blepharitis present. Complicated by seborrhoeic dermatitis. Organisms, *Staph. aureus*. 11,340 units (sodium salt in lanette base, 400 units per g.) in 21 days (applied twice daily). Improvement till 11th day, then complete relapse, so that face was "worse than ever before." Further slight improvement just before treatment was stopped. Culture from a pustule at this stage showed that the organism had increased its resistance to penicillin. Given *x* rays (50 *r* twice) with some improvement. Two weeks later a second course, using solution of calcium penicillin (1,000 units per c.cm.), was started. 38,410 units in 15 days. Face sprayed 4 times daily (right side only for first 7 days). After this both sides seemed to be cured. Solution then applied to eyes (2 drops into each, 4 times daily), 22,470 units being given in 21 days. Blepharitis cured a few days before treatment was stopped. Face began to relapse only a few days after treatment to the eyes was finished. After 2 weeks there was a return of the blepharitis. Condition was stationary for the next 6 weeks under treatment with pyrogallol in zinc cream.

Case 8.—M., aged 40. Duration 2½ years. No response to quinoline, nasal operations, *x* rays, or sulphonamides. Infection of skin localized to upper lip and eyelids, but chronic purulent nasal discharge present. Organisms, *Staph. aureus* and *Strep. pyogenes*. 11,970 units (sodium salt in lanette base, 400 units per g.) in 21 days (applied twice daily). Gradual improvement for 15 days, then complete relapse. Organisms showed some increase in resistance to penicillin. Quinoline emulsion and *x* rays produced some improvement during next 2 weeks. Second course then started. 118,750 units (solution of calcium salt, 1,000 units per c.cm.) in 19 days. Solution sprayed on to upper lip and up nose 4 times daily. Improvement for 11 days, then complete relapse; the solution appeared only to irritate the lesions.

Case 9.—M., aged 38. Duration 2½ years. Sulphonamides and local applications ineffective. Scattered lesions, associated with seborrhoeic dermatitis. Organisms, *Staph. aureus*. 5,600 units (sodium salt in lanette base, 400 units per g.) in 8 days (applied twice daily). Complete cure. Relapse began after 2 weeks and became severe after 4 weeks. Treated by 49,950 units (solution of calcium salt, 1,000 units per c.cm.) in 15 days. Sprayed on twice daily. Complete cure. Relapse after 5 days. Seen 6 weeks later, the condition was not severe, although he had had no further treatment.

Case 10.—M., aged 31. Duration 3 years. Only temporary improvement with *x* rays and local applications. Lesions worst on chin and forehead. Some crusting. Organisms, *Staph. aureus*. 17,625 units (calcium salt solution, 1,000 units per c.cm., and in lanette base, 400 units per g.) in 14 days. Sprayed 4 times daily for 3 days, then twice daily. Ointment only for last 2 days. Almost cured. Cure completed after application of a further 6,000 units in 2 weeks. Began to relapse a few days later. During 2nd and 3rd weeks after start of relapse he used another 12,000 units, but the ointment only irritated his skin, and no progress was made.

Case 11.—M., aged 32. Duration 3 months. Sulphonamides and other local applications ineffective. Organisms, *Staph. aureus*. 24,970 units (sodium salt in lanette base, 400 units per g.) in 27 days (applied twice daily) produced complete cure. Relapsed a few days later. Eight weeks later his condition was not severe, though other methods of treatment had been employed in the interval.

Case 12.—M., aged 47. Duration 2½ years. All local applications ineffective. Lesions scattered over beard area, but mostly in midline. Organisms, *Staph. aureus*. 139,860 units (solution of calcium salt, 1,000 units per c.cm.) in 28 days. Sprayed thrice daily. Complete cure. There was minimal improvement for the first 5 days, but cure was almost complete after 18 days.

Case 13.—M., aged 27. Duration 5 years. Only temporary improvement with numerous local applications, 2% crystal violet being the most useful. Severe crusting of upper lip; eyelids and left eyebrow also affected. Chronic sinusitis. Organisms, *Staph. aureus*. 67,190 units (solution of calcium salt, 1,000 units per c.cm.) in 15 days. Sprayed on thrice daily. There was a gradual but steady improvement. Had to be discharged for domestic reasons, and was given 12,000 units as ointment with which to continue treatment.

Case 14.—M., aged 23. Duration 1½ years. Recent exacerbation. Temporary improvement with quinoline emulsion. Generalized rash all over beard area; some impetiginous lesions also. Organisms, *Staph. aureus*. 50,000 units in 15 days. Solution of calcium salt sprayed on thrice daily. Complete cure, which has now lasted one week.

Case 15.—M., aged 21. Duration several months. Only temporary improvement with quinoline emulsion. Generalized rash, but predominant on chin. A few impetiginous lesions present. Organisms, *Staph. aureus* and *Strep. pyogenes*. 40,920 units in 12 days. Solution of calcium salt sprayed on thrice daily. Complete cure.

Commentary

In judging these results it is necessary to remember that most of the cases were chosen for the very reason that they were of long duration or had notably failed to respond to ordinary methods of treatment.

Analysis of results shows that: (*a*) Five cases (Nos. 4, 6, 12, 14, 15) were initially cured and have remained so. These cures have lasted for periods up to 19 weeks. (*b*) Three cases (Nos. 1, 2, 3), though initially cured, relapsed after periods varying from 10 days to 5 weeks. Their relapses were cured, and cures have now lasted for periods varying from 9 to 22 weeks. (*c*) Five cases (Nos. 5, 7, 9, 10, 11), though initially cured, relapsed after periods varying from a few days to 15 weeks, and their relapse remains uncured. (*d*) One case (No. 8) was never cured. In one case (No. 13) treatment is still in progress.

The remarkable initial response in the first 6 cases which we treated was perhaps unfortunate, as it led to false confidence in the method of application. It became clear subsequently that the ointment used could in some cases lead to irritation of the skin, though which constituent of the

ointment was responsible is not at present clear. The comparative impurity of present supplies of penicillin must be remembered as a possible cause. Further investigations on methods of application are clearly indicated, but even if the ideal method is found it still appears that recurrences in some cases may be frequent. The tendency of cases of sycosis barbae to relapse after apparent cure is well known, and there is no reason to suppose that penicillin can abolish this inherent tendency. The most to be expected of penicillin is that it may cure established infection or, if applied prophylactically, prevent reinfection. Established infection was indeed cured, though sometimes only temporarily, in all but one of this series. In the exception (Case 8), failure was probably due to a continual reinfection from the nasal discharge. It may be noted here, in connexion with associated disease, that all three patients who also suffered from seborrhoeic dermatitis relapsed within 14 days of cure.

The significance of the increase in resistance to penicillin displayed by the organisms in Cases 7 and 8 is doubtful; this also requires further elucidation. The use of solution is not recommended except perhaps in cases irritated by the ointment, as it tends to be extravagant of penicillin and does not appear to produce final cure any more quickly. There is sometimes, however, a more dramatic response during the first few days. Twice-daily spraying is probably adequate. The solution seemed to irritate the skin in Case 8.

Treatment should in all cases be continued for a few days after apparent cure; in our cases penicillin was probably stopped earlier than was desirable, owing to the need for economy in its use. When it becomes freely available it should be possible to start treatment at the first signs of a relapse or even to use penicillin prophylactically.

This series is a small one, and further experience may show that we have been unduly fortunate in our results. Even if this proves to be the case, it is clear that, while penicillin can by no means be relied upon to produce a lasting cure in all cases of sycosis barbae, it can in individual cases produce results unobtainable by any other means. If only for this reason, it has a definite place in the treatment of the disease.

Impetigo (12 Cases)

Some of these were primary impetigo and others were secondary to disease such as scabies. All were treated by removal of crusts followed by local application of sodium or calcium penicillin in the lanette wax and petroleum jelly base, 400 units per g.

Case 1.—M., aged 7. Duration 7 days. Upper lip, cheeks, and backs of hands predominantly affected. Organisms, *Strep. pyogenes*. 1,800 units in 9 daily applications. Single lesions healed in 2 to 3 days; cure complete in 9 days.

Case 2.—M., aged 19. Duration 20 days. Extensive crusting of face, ears, arms, buttocks, and thighs. Organisms, *Strep. pyogenes* and *Staph. aureus*. 8,505 units in 21 daily applications. Only one area was treated at a time, so final cure was delayed; individual areas were cured after 4 to 6 days' treatment.

Case 3.—F., aged 4. Duration 11 months. Associated with seborrhoeic dermatitis, and affecting scalp and ears. Organisms *Strep. pyogenes* and *Staph. aureus*. 18,900 units in 21 daily applications. Rapid improvement for 10 days; condition then became stationary. The improvement coincided with elimination of the secondary infection, the seborrhoeic dermatitis being unaffected by further treatment.

Case 4.—M., aged 1. Duration 5 weeks. Associated with scabies, and affecting face and ears. Organisms, *Strep. pyogenes* and *Staph. aureus*. 2,800 units in 11 days (applied twice daily). Single lesions healed in 3 to 4 days; cure complete in 11 days.

Case 5.—M., aged 10. Duration 10 days. Face only affected. Organisms, non-haemolytic streptococci and *Staph. aureus*. 3,960 units in 9 days (applied twice daily). Single lesions healed in 4 days; cure complete in 9 days.

Case 6.—M., aged 4. Duration 12 days. Face, ears, and legs. Organisms, *Strep pyogenes*. 14,000 units in 8 daily applications. Single lesions healed in 3 days; cure complete in 8 days.

Case 7.—F., aged 6 months. Duration 14 days. Associated with seborrhoeic dermatitis and scabies, and affecting scalp, trunk, and limbs. Organisms, *Staph. aureus*. 16,560 units in 6 daily applications. Complete cure of impetigo. Relapsed after 15 days. Cured by application of 7,360 units in 8 days.

Case 8.—F., aged 5. Duration 3 weeks. Associated with scabies, and affecting lower limbs. Organisms, *Strep. pyogenes* and *Staph. aureus*. 12,000 units in 8 days (applied twice daily). Single lesions healed in 5 days; complete cure in 8 days.

Case 9.—M., aged 37. Duration 12 days. Extensive crusting of face. Organisms, *Staph. aureus*. 24,000 units in 12 daily applications. Great improvement in 5 days; cure complete in 12 days.

Case 10.—M., aged 24. Duration 14 days. Scalp, neck, and forearms affected. Organisms, *Staph. aureus*. 11,960 units in 12 days (applied twice daily). Scalp cured in 4 days; other areas required 12 days.

Case 11.—M., aged 27 years. Duration 10 days. Face, scalp, and arms. Conjunctivitis and blepharitis. Organisms, *Staph. aureus* and diphtheroids. 8,170 units in 19 daily applications to face, scalp, and arms. (Eyes also treated—see "Blepharitis," Case 5.) Almost well in 5 days, but even by the 19th day a few new lesions were appearing.

Case 12.—F., aged 3½ months. Duration several weeks. Scalp, face, and hands affected. Underlying eczema of scalp and face. Organisms, haemolytic streptococci. 24,000 units in 15 daily applications. Impetigo cured in 5 days; 10 days' further treatment had no beneficial effect on the eczema.

Commentary

It will be seen that of 12 cases treated 11 were completely cured. The important factor is the time required to produce this result: on an average this was 8 to 9 days. Most of these patients, however, were in a fairly advanced condition when treatment was started, and as ointment was applied only in the immediate neighbourhood of the lesions it was difficult to prevent spread to unaffected areas. Individual lesions under treatment healed in about 4 days.

Minor variations in the routine of treatment do not seem to be of much importance: for instance, one application of ointment a day appears as effective as two. But when penicillin becomes more easily obtainable it may be possible, by spreading it more widely, to prevent formation of new lesions and materially accelerate complete cure.

We consider that penicillin can be more generally relied upon to produce a rapid cure than can quinoline emulsion or sulphonamides, though these drugs may in individual cases be equally successful.

In view of discussions regarding the bacteriology of impetigo it is worth noting that in these 12 cases the infecting organisms were: in 3 cases, *Strep. pyogenes* alone; in 3 cases, *Staph. aureus* alone; in 4 cases, *Staph. aureus* and *Strep. pyogenes*; in 1 case, *Staph. aureus* and non-haemolytic streptococci; in 1 case, *Staph. aureus* and diphtheroids.

Eczema (9 Cases)

For the most part the patients treated were resistant cases of chronic eczema in which it seemed that elimination of secondary infection might aid recovery. All were treated with sodium or calcium penicillin in the lanette wax and petroleum jelly base, 400 units per g.

Case 1.—M., aged 27. Duration several weeks. Large raw areas on hands, forearms, face, and ears, resistant to all previous treatments. Organisms, *Staph. aureus*. 29,070 units in 21 daily applications. Notable improvement, patient being left with a residual dry eczema, which responded to ordinary methods of treatment.

Case 2.—F., aged 67. Duration 10 days. Severe weeping eczema of wrists and hands with purulent blisters. Organisms, *Strep. pyogenes* and *Staph. aureus*. 16,000 units in 13 days to right hand only (applied twice daily). Left side treated with zinc cream. Right hand cured after 11 days, left after 13 days.

Case 3.—M., aged 35. Duration 6 months. Dry scaly eczema of face, neck, and ears with fissuring. Organisms, *Strep. pyogenes* and *Staph. aureus*. 39,200 units in 7 daily applications to right side only. Great improvement after 3 days, whereupon base alone was applied to left side. This resulted in similar but less rapid improvement. Subsequent application of base without penicillin to both sides effected cure, but relapse occurred a few weeks later.

Case 4.—M., aged 20. Duration 4 days. Vesicular eczema of left index, with pustules on rest of hand. Organisms, *Staph. aureus*. 24,000 units in 10 daily applications. No improvement in eczema.

Case 5.—M., aged 23. Duration 16 years. Generalized eczema with fissures. Organisms, *Staph. aureus* and another Gram-positive coccus. 36,000 units in 20 days (applied twice daily) to face and neck only. Fissures healed. Otherwise unaffected.

Case 6.—M., aged 2½. Generalized infantile eczema dating from birth. Organisms, *Strep. pyogenes* and *Staph. aureus*. 30,100 units in 22 days (applied twice daily). No change for 5 days; thereafter

steady improvement. Began to relapse 2 to 3 days after treatment stopped.

Case 7.—M., aged 25. Duration 3 weeks. Face predominantly affected. Sterile on culture. 6,000 units in 15 daily applications. Cured.

Case 8.—M., aged 8 months. Duration 4½ months. Scalp and left cubital fossa. Organisms, *Strep. pyogenes* and *Staph. aureus*. 12,040 units in 14 daily applications. Improved for 5 days, then relapsed. (Prevention of scratching was very difficult.)

Case 9.—M., aged 58. Duration 8 months. Large raw weeping patch below the knee. Organisms, *Staph. aureus* and *Strep. pyogenes*. 71,810 units in 22 days (applied twice daily). Healed; only a residual redness persisted.

Commentary

Cases 3 and 7 suggest that such improvements as occurred in this series were possibly due to the lanette base rather than to penicillin. There is little doubt, however, that in Cases 1 and 9 the dramatic improvement was the result of controlling the infection, and the limited success in Cases 5 and 6 is in agreement with this. Penicillin should be worthy of trial in cases of eczema with evidence of secondary infection.

Blepharitis (8 Cases)

This condition has been mentioned in connexion with sycosis barbae; the cases now to be described were, however, not accompanied by sycosis. They were treated by application of sodium salt in lanette wax and petroleum jelly base, 400 units per g., to the lids, or by instillation of solution of sodium or calcium penicillin into the eye. All cases were bilateral. The results of treatment are in general agreement with those obtained by Florey and Florey (1943).

Case 1.—F., aged 3. Duration 5 months. Eyebrows also infected. Organisms, *Neisseria catarrhalis, Strep. pyogenes,* and *Staph. aureus*. 1,640 units (ointment) in twice-daily applications for 3 days. Cured. Relapsed after 10 days. 2,870 units in twice-daily applications for 7 days. Cured. Relapse after 3 weeks. *Staph. aureus* found to be less sensitive than previously. 6,000 units in daily applications for 15 days. Cured in 10 days. Slight relapse about 3 weeks later. When seen 8 weeks after treatment was stopped the right eye showed a mild blepharitis and the left appeared cured. The only treatment had been local application of petroleum jelly.

Case 2.—M., aged 35. Duration 28 years. Organisms, *Staph. aureus*. 5,800 units (sodium salt in saline, 500 units per c.cm.) in 10 days. Two drops 2-hourly by day into left eye only, for 6 days. Great improvement in left eye. Then both sides treated. Cure in 10 days. Relapsed after a few weeks.

Case 3.—F., aged 30. Duration 2½ years. Seborrhoeic dermatitis present. Organisms, *M. tetragenus* and *Staph. aureus*. 1,400 units in daily applications for 7 days. Cured.

Case 4.—M., aged 22. Duration 3½ years. Bilateral conjunctivitis. Organisms, *Staph. aureus*. 8,920 units in 12 days. Two drops of sodium salt solution in saline (500 units per c.cm.) into each eye 2-hourly by day. Ointment also applied to lids nightly, but discontinued owing to intense irritation produced. Thereafter solution was applied to lids on a swab instead. Complete cure, which has now lasted 11 weeks.

Case 5.—M., aged 27. Duration 9 days. Impetigo and conjunctivitis also present. Organisms, *Staph. aureus* and diphtheroids. 3,800 units (ointment) in daily applications over 19 days. Cured. (Impetigo also treated—see "Impetigo," Case 11.)

Case 6.—M., aged 26. Duration 14 years. Organisms, *Staph. aureus*. 8,000 units (solution of calcium salt, 1,000 units per c.cm. —2 drops 2-hourly by day into each eye) in 5 days. Cured. Has now remained cured for 9 weeks.

Case 7.—F., aged 43. Duration 3 weeks. Associated with pemphigus vulgaris. Organisms, *Staph. aureus*. 2,340 units in twice-daily applications for 5 days (ointment). Cured. Relapsed after 10 days. 6,500 units in 13 days. Cured. Seven weeks later there was only a slight residual redness of the lids (but the pemphigus had also improved).

Case 8.—M., aged 32. Duration 2 weeks. Organisms, *Staph. aureus*. 3,150 units in twice-daily applications of ointment over 9 days. Cured. Slight relapse 6 days later. 2,800 units applied in 8 days. Cured. No relapse when seen 7 days later.

Commentary

Previous experience with conjunctivitis had led us to expect that solution of sodium salt in saline (500 units per c.cm.) would be less irritant to the eye when used as drops than aqueous soloutions of calcium salt (1,000 units per c.cm.). Patient No. 6, however, did not find the latter uncomfortable, and it seems that individuals vary in their tolerance. The application of ointment to the lids was not usually productive of any reaction, though in Case 4 it did produce a marked aggravation of the blepharitis.

Blepharitis being generally extremely resistant to treatment, the initial response of these cases is most encouraging. The frequency of relapse is at present a disappointing feature, but when supplies of penicillin are better it may be possible to prevent relapse by, for example, a nightly application of the drops.

Otitis Externa (7 Cases)

These cases were treated by sodium penicillin in lanette wax and petroleum jelly base (400 units per g.) or by solution of calcium penicillin (1,000 units per c.cm.). Where the solution was used, drops were introduced into the external meatus thrice daily, and it was then plugged with cotton-wool or petroleum jelly gauze.

Case 1.—M., aged 45. Bilateral. Duration 7 months. Organiisms, *Staph. aureus,* diphtheroids, coliforms, and an unidentified Gram-positive coccus. 36,870 units (solution) in 7 days. After 5 days there was an improvement, and sensitive organisms were no longer present. Before treatment was finished, however, there was a relapse.

Case 2.—M., aged 56. Bilateral. Duration 2 years. Organisms, diphtheroids, coliforms, and *B. proteus*. 89,665 units (solution) in 22 days (twice daily only during final 7 days). Number of sensitive organisms diminished, but there was only improvement—not cure. Nineteen weeks later his improved condition was still being maintained.

Case 3.—M., aged 41. Right side only. Duration 35 years. Organisms, *Staph. aureus,* diphtheroids, and coliforms. 18,765 units in 8 days (solution). No sensitive organisms after second day. Cured in 5 days; relapsed 5 days later.

Case 4.—F., aged 23. Bilateral. Duration 5 months. Organisms, *Staph. aureus* and coliforms. 6,000 units in 22 days (ointment, applied twice daily). Complete cure. Discharged to use another 6,000 units. No relapse reported after 10 weeks.

Case 5.—M., aged 31. Bilateral. Duration 1½ years. Organisms, streptococci, *Staph. aureus, B. proteus,* and diphtheroids. 74,000 units in 14 days (solution twice daily only for last 5 days). Clinical cure by 5th day, but bacteriology still unaltered by 10th day.

Case 6.—M., aged 39. Bilateral. Duration 14 months. Organisms, *Staph. aureus, Strep. faecalis,* diphtheroids, and coliforms. 3,000 units in 15 daily applications of ointment. Cured. Relapsed 17 days later. A more resistant collection of organisms found. 6,000 units in 22 daily applications. Improvement but no cure.

Case 7.—M., aged 25. Bilateral. Duration 3 weeks. Organisms, *Staph. aureus* and coliforms. 6,000 units in 15 daily applications of ointment. Cured.

Commentary

These infections have all been mixed, and without exception part of each flora has been insensitive to penicillin. The incidence of incomplete cures and early relapses is therefore not surprising. Ointment is a simpler and more economical method of treatment than the solution, and appears to be equally effective.

Boils (5 Cases)

These were treated with sodium penicillin in lanette base, 400 units per g.

Case 1.—M., aged 31. Recurrent furunculosis of buttocks of 13 months' duration. Organisms, coagulase-negative *Staph. albus*. 21,000 units in 12 daily applications effected cure before end of treatment. Used a further 12,000 units after discharge. No relapse 12 weeks later.

Case 2.—M., aged 10. Boils on back of neck of 3 weeks' duration. Organisms, *Staph. aureus*. 4,050 units in 14 days (applied twice daily). Slight improvement only.

Case 3.—M., aged 65. Axillae chiefly affected. Duration 2 months. Organisms, *Staph. aureus*. 3,500 units in 2 daily applications. Cure, lasting now 11 weeks.

Case 4.—M., aged 15. Neck and chin. Duration 2 days. Organisms, coagulase-negative staphylococci. 6,090 units in 15 days (applied twice daily). Cured.

Case 5.—M., aged 24. Large discharging boils on buttocks. Duration uncertain (mentally defective). Organisms, *Strep. pyogenes* and *Staph. aureus*. 24,000 units in 15 daily applications. Healed. No new lesions.

Commentary

Patient No. 3, the only apparently spectacular cure, was recovering from existing lesions when treatment was started; the fact that no further lesions have appeared may be due to penicillin. These cases suggest that penicillin may possibly

be useful in stopping a series of recurrent boils. Probably the solution would have been more effective than the ointment, although more extravagant. Penicillin applied externally appeared to have no effect whatever on the evolution of an individual boil.

Acne (3 Cases)

Case 1.—M., aged 23. Pustular acne of face, neck, chest, and back of 8 years' duration. Culture sterile. 15,000 units (sodium salt in lanette base, 400 units per g.) in 12 days (applied twice daily). Very slight improvement.

Case 2.—M., aged 22. Pustular acne of face, back, and chest. Duration 6 years. Organisms, *Staph. aureus*. 37,060 units (sodium salt in lanette base, 400 units per g.) in 34 daily applications to left side of back only. Improvement for first 10 days ; thereafter i.s.q.

Case 3.—M., aged 40. Acne conglobata of 5 years' duration. Arms, chest, and back extensively affected. Organisms, *Staph. aureus*. 235,320 units in 29 days. Solution of calcium salt (1,000 units per c.cm.) was sprayed on 4 times daily. Cured. Gradual relapse began after 7 days.

Commentary

Since greasy creams are in any event unsuitable for application to cases of acne, and since treatment in Case 3 was temporarily successful, it might have been better to use solution in Cases 1 and 2 also. The method is, however, extravagant. The value of penicillin in this condition remains uncertain. The acne bacillus is resistant to penicillin, and the response of the disease to treatment will depend presumably on the extent to which staphylococci are accountable for the suppuration in each particular case.

Miscellaneous

The following results are recorded for the sake of completeness, but it is not possible to draw any conclusions of value from them. The ointment was used unless otherwise stated.

Two cases of generalized seborrhoeic dermatitis were treated ; one failed to respond with ointment, but recovered temporarily when solution was sprayed on to affected areas ; the other responded to ointment only in areas where secondary infection was marked. A third case, in which the disease was confined to the scalp, cleared up well when treated with ointment. (Staphylococcal secondary infection was present.) One small carbuncle which was discharging healed in 12 days under treatment with ointment. A case of Bockhart's impetigo accompanied by boils was improved, but the boils were hardly affected. A case of dermatitis repens (Crocker) failed to respond. Four cases of chronic ulceration of the lower limb of uncertain aetiology were all improved. Two cases of varicose ulceration were treated ; one patient failed to respond, and the other, who was suffering from varicose eczema as well, was greatly benefited. One case of psoriasis, one case of herpes labialis, and one case of pemphigus vulgaris were unaffected.

Summary

The treatment of 75 cases of skin disease by local application of penicillin is described.

The drug is of obvious value in sycosis barbae, impetigo, and blepharitis. It is also effective in some cases of chronic eczema with secondary infection and in some cases of otitis externa.

REFERENCE

Florey, M. E., and Florey, H. W. (1943). *Lancet*, **1**, 387.

The World's Children (published by the Save the Children Fund, 20, Gordon Square, W.C.1 ; 6d.) now reverts to its former character as a "journal of child care and protection considered from an international viewpoint." The more domestic news of the Fund, in whose interest the magazine is published, is relegated to an appended "Current Chronicle." International interests include an article on the United Nations Relief and Rehabilitation Administration, by Gladys Skelton. Sylvia Thompson expands her suggestion that the best war memorial would be the interchange of young people between the different countries to help to promote world understanding; and Lillian de Lissa, describing wartime care of children in the United States, stresses the eagerness of the Americans to profit by Great Britain's wartime experience in the nursery schools field. Elsa Castendyck discusses the causes of juvenile delinquency. The German system of food rationing is revealed in a table showing the provision of essential foods for various age groups of children. The effects of the war on the rising generation in Europe are seen through Swiss eyes by Dr. Georges Thélin of Geneva.

THE LABORATORY CONTROL OF PENICILLIN TREATMENT

BY

LAWRENCE P. GARROD, M.D., F.R.C.P.

The bacteriological laboratory has very heavy duties in connexion with the clinical use of penicillin, and where many cases are being treated it is strongly advisable that someone in the laboratory should be enabled to devote almost whole time to the necessary work. This work falls into three main categories: the preparation of solutions, etc., bacteriological diagnosis, and observation of the results of treatment by various *in vitro* tests.

The methods of preparing penicillin for clinical use employed in this and other present research centres are described in a forthcoming M.R.C. Memorandum, and cannot be given in detail here. Penicillin is supplied in the form of powder or tablets ; solutions of various strengths have to be prepared from this, and sometimes diluted powders or creams. In the performance of this work two properties of penicillin should be constantly borne in mind. It is a very labile substance, liable easily to lose its activity under adverse conditions. It is also not an ordinary antiseptic, capable of destroying any bacteria with which it may become contaminated ; on the contrary, there are many species quite unaffected by it which will not only remain alive in solutions of penicillin but may even decompose them, with consequent loss of activity. These two properties call for high standards of precaution in handling during preparation and for exceptional safeguards during subsequent use.

A refrigerator is the only suitable place to keep solutions and creams before and during use. We have also found it advisable that each patient under local treatment should have his own bottle of solution, owing to the danger of contamination in the ward: this has been known to occur by withdrawing the contents with a syringe and needle or tubing which has already been used for aspirating the lesion. Penicillin can easily become a vehicle of cross-infection, and surplus solution returned after use to the laboratory has occasionally been found grossly turbid owing to the presence of pus and living bacteria.

Initial Bacteriological Diagnosis

Penicillin is effective only against certain bacteria, and it is therefore necessary to know the nature of the infection before embarking on treatment with any confidence in its result. In characteristic conditions having only one usual microbic cause, such as impetigo and sycosis, this may appear superfluous in routine treatment, but even here it may be advantageous, since it is advisable to know not only the species of micro-organism concerned but the sensitivity of the particular strain to penicillin ; in some species, particularly staphylococci, this is variable. An exact but time-consuming method is to isolate the responsible pathogen in pure culture and inoculate broth containing various low concentrations of penicillin to determine the least which will inhibit growth. A much more rapid method, quite satisfactory for most purposes, which furnishes both a species and a sensitivity diagnosis from one primary culture, is Fleming's agar cup method. One or two circular holes are punched in a blood agar plate with a sterile cork-borer, and, after inoculation and spreading, a drop of weak penicillin solution (10 units and 1 unit per c.cm.) is pipetted into each hole. Penicillin diffuses into the surrounding medium, where its concentration varies inversely with distance from the cup ; the width of the zone surrounding the cup in which no colonies appear is thus a measure of the sensitivity of the organism. In mixed cultures two zones are often evident—an inner containing no growth, and an outer containing colonies of only one more resistant species. Both for an expeditious diagnosis and for dealing with many cases this method is invaluable. The following observations on the sensitivity of different species have been made by this and other methods.

Gram-positive Cocci.—As previously reported by others, we have found occasional strains of otherwise typical *Staph. aureus* abnormally resistant to penicillin. This was sometimes

a property of the original culture, but more often it developed during treatment, clearly owing to habituation; there was corresponding failure of clinical progress. No resistant strain of *Strep. pyogenes* or of *Pneumococcus* has been encountered. The widely varying susceptibility originally reported by the Oxford workers for both *Pneumococcus* and *Strep. viridans* is not borne out by our experience; no really resistant strain of either has been found. *Strep. faecalis* (enterococcus), on the other hand, is always highly resistant.

Mouth Bacteria.—Observations made mainly in connexion with work described in an earlier paper (p. 517) by Mowlem have led to the conclusion that the great majority of the very numerous bacterial species found in the mouth are penicillin-sensitive. This is of far-reaching practical importance, since it means that infections derived from or connected with the mouth are in general susceptible to penicillin treatment, just as those connected with the bowel are insusceptible owing to the prevalence there of resistant species. The flora of the mouth is highly complex and has been imperfectly studied; the following observations are therefore perforce of an elementary nature. In plates, both aerobic and anaerobic, inoculated with material from osteomyelitis of the jaw, from infected compound fractures of the jaw, and from infected gums, or with saliva, the only organisms ever found markedly resistant to penicillin as judged by the cup method have been *Monilia albicans*, an occasional *Neisseria*, and *Haemophilus*. Whole groups of bacteria which are thus sensitive in doubtless varying but apparently adequate degrees are aerobic streptococci (including various types of *Strep. viridans*), anaerobic streptococci, anaerobic Gram-negative bacilli (*F. fusiformis* and many others unidentified), and various Gram-positive bacilli. The mixed and predominantly anaerobic flora often found in infections derived from the mouth is thus in general sensitive to penicillin, and the results of treatment are as would be expected from this.

Actinomyces.—According to the Oxford workers, *Actinomyces* is penicillin-sensitive and actinomycosis susceptible to treatment. We have examined 5 strains, determining their sensitivity by cultivation in a series of broth tubes containing falling concentrations of penicillin, an identical series being inoculated with the Oxford H strain of *Staph. aureus* as a control; the former series was incubated anaerobically for 10 days, during which time it is probable that some of the penicillin activity of the medium was lost. Two strains had approximately the same degree of sensitivity as the standard staphylococcus; they were obtained from cases of actinomycosis of the face, and both appear to have responded well to local treatment. Another, forming a much more compact and firm colony, was 8 times more resistant; the jaw lesion from which it was derived did not respond to local treatment with penicillin. A fourth strain, from a patient with thoracic actinomycosis who died of *Ps. pyocyanea* septicaemia during systemic penicillin treatment, was 4 times as resistant as the staphylococcus. The fifth strain grows normally only in concentrations tolerated by the staphylococcus, but sparsely and atypically in concentrations up to 16 times greater: this case (jaw) has not been treated. The sensitivity of *Actinomyces* evidently varies, possibly to a greater extent than observations by this method reveal.

We have had no occasion to examine the sensitivity of strains of other susceptible bacteria, such as the various *Clostridia*, *B. anthracis*, and *C. diphtheriae*.

Mixed Infections.—It has sometimes to be decided whether a mixed infection including sensitive and resistant bacteria is suitable for treatment. The latter are usually Gram-negative bacilli, and much appears to depend on whether they are active producers of penicillinase and may thus destroy the penicillin in the lesion. *Proteus* does not produce penicillinase, and combined infections by this organism and staphylococci have been treated successfully in this series; the cocci disappear, and although *Proteus* remains the condition improves, suggesting that the coccus has played the more important part in maintaining the infection. On the other hand, combined infection by a pyogenic coccus and a penicillinase-producing coliform bacillus may be quite unaffected; in one such case, the lesion being a cavity in which solution could be well retained, haemolytic streptococci persisted in undiminished numbers. That the reason for this was the destruction of penicillin by the coliform bacillus in the wound fluid was proved by repeatedly demonstrating that on withdrawal after 24 hours the penicillin content of this fluid was *nil*.

Examinations to Check the Results of Treatment

Swabs or other specimens have been obtained daily, and sometimes at longer intervals later, which were cultivated in order to follow the effect of treatment. When this is successful, immediately scantier growths are succeeded by total sterility. The results obtained in 60 miscellaneous cases treated locally are given in Table I. This includes only wounds (not skin diseases)—cases in which there was a simple infection by staphylococci or haemolytic streptococci, or both—and excludes a series of cases with extensive bone involvement, such as old compound fractures (see Robertson, p. 519), in which we now know this method of treatment to be useless.

TABLE I.—*Response to Local Treatment of Wounds*

Nature of Lesion	No. of Cases	No. of Cases Infected with		Days before Negative Swab (No. of Cases)												No. of Cases developing Secondary Infection	
				Strep. pyogenes						Staph. aureus							
		Str. pyog.	St. aur.	1	2	3–4	5–7	8–14	Failures	1	2	3–4	5–7	8–14	Failures	Ps. pyocyanea	Proteus
Superficial and accessible wounds (chiefly operations for plastic repair)	33	10	27	2	1	3	2	1	1	0	3	7	10	5	2	6	2
Sutured wounds treated through tubes	11	4	11	2	1	—	—	—	1	1	1	2	3	1	3	4	—
Sinuses	16	5	15	4	—	1	—	—	—	1	—	4	2	2	6	3	1
Totals	60	19	53	8	2	4	2	1	2	2	4	13	15	8	11	13	3

The variability of effect seen in Table I probably depends largely on the structure of the lesion, and thus on the feasibility of permeating it with penicillin completely and maintaining this condition. *Strep. pyogenes*, as would be expected from its greater sensitivity, tends to disappear earlier than *Staph. aureus*. Secondary infection with *Ps. pyocyanea* or *Proteus* often developed during treatment in these and other cases, and aroused a suspicion in some minds that penicillin not only fails to inhibit the growth of these organisms but actually stimulates it. Experiments to determine whether this is so are not complete.

Estimation of the Penicillin Content of Exudates

Since therapeutic effect depends on maintaining an adequate concentration of penicillin in the lesion, it is useful to know whether this condition has been secured. If solution is being introduced into an abscess or other cavity, pus can be withdrawn before a further injection is made and its penicillin content determined. This is done by placing it in a cup in an agar plate heavily inoculated with the standard staphylococcus; growth is inhibited in a zone around the cup the width (radius) of which is a measure of penicillin concentration (concentrations of 100, 10, and 1 unit per c.cm. produce zones measuring 20, 12, and 3 mm. in width respectively).

Persistence is most regularly to be expected in closed cavities treated by aspiration and injection. This fact is illustrated by estimations of penicillin content in pus from empyemas so treated: in 14 specimens of pus withdrawn 2 days after the first injection the mean inhibition zone was 9 mm., and after 3 days (7 specimens) 7 mm. In one case pus giving a 6-mm.

zone was withdrawn 5 days after the last injection. Zones of 2 mm. have been observed after 9 and even 11 days, but their significance is doubtful, since pus containing no penicillin has been observed sometimes to produce this degree of inhibition.

Specimens of fluid from other lesions examined in this way total 192. Some of these were from abscesses treated by aspiration and injection with results comparable to those in empyema. The majority were withdrawn either from sinuses or from recent operation wounds sutured over a tube. Table II records the penicillin content in 106 such specimens; only those obtained one day after treatment are included, and others are excluded in which it appeared that penicillin was being destroyed by coliform bacilli.

TABLE II.—*Zones of Inhibition produced by Fluids withdrawn One Day after Local Treatment with Penicillin Solution (usually 1,000 Units per c.cm.)*

	No. of Cases giving Zones (in mm.) of					
	0	1–3	4–6	7–10	11–15	16–21
Sinuses ..	10	2	3	5	4	1
Wounds ..	18	11	5	5	10	32
Totals ..	28	13	8	10	14	33

Mechanical factors favouring retention again appear paramount in determining results. It is possible that the vascularity or other properties of the tissue bordering a cavity have also some influence, but clear evidence of this has not been obtained.

Estimations of Penicillin Content of Blood

During systemic treatment the penicillin content of the blood should be estimated. This is possible only by determining the bacteriostatic power of the serum either for the patient's own organism or for the standard staphylococcus. All methods for doing this depend on using the undiluted patient's serum and dilutions of it in normal serum as a culture medium; a small inoculum of staphylococci grows in serum in the form of colonies, which may be counted if such cultures are made on slides, the cover-slip being sealed with petroleum jelly. Inhibition of growth in any given dilution may be either complete (no colonies) or partial (fewer colonies than in a normal serum control).

Dosage in this series of cases was uniform, 120,000 units a day being given to adults and a correspondingly smaller dose, approximately related to body weight, in children. The penicillin content of 37 specimens of blood from 13 patients receiving penicillin by intravenous drip or other continuous method of administration is stated in Table III.

TABLE III.—*Numbers of Serum Specimens Bacteriostatic to Oxford H Staphylococcus in Different Dilutions*

Bacteriostasis:	
Nil in pure serum	1
Partial in pure serum	5
Complete in pure serum	11
Partial in 1 in 2 serum	3
Complete in 1 in 2 serum	7
,, ,, 1 in 4 serum	5
,, ,, 1 in 8 or over	5

These variations cannot be fully explained, although one cause of a high titre may certainly be retention due to renal inefficiency; 3 of the 5 specimens listed as "1 in 8 or over" came from the case referred to also by Morgan, Christie, and Roxburgh (p. 515), in which repeated estimations (not listed here), after administration was stopped, showed long delay in excretion. A concentration giving complete inhibition in pure serum is probably adequate for full therapeutic effect, and *in vitro* tests (to be published later) have shown that the rate of death of staphylococci in blood containing penicillin is not accelerated by increasing the penicillin concentration within the range of 0.1 unit to 10 units per c.cm.

When three-hourly intramuscular injections are given, the blood concentration is known to rise rapidly after each injection, then to fall progressively until the next. Specimens obtained immediately before a dose was due gave no inhibition at all in 6 and partial inhibition in pure serum only in 3. A much greater number of such estimations must form the basis of any judgment on this method of treatment; but to gain an idea of whether dosage is adequate must clearly be more difficult, and on theoretical grounds the maintenance of a steady level by continuous administration seems to me more likely to achieve full therapeutic effect.

Comment

This condensed account of laboratory work on cases some of which are described by foregoing authors is no more than an interim report on a study still in progress. It is intended to present a picture of the nature and volume of work which is called for from the laboratory if penicillin treatment is to be directed intelligently and, still more, if its efficiency is to be improved. At the same time a few minor original observations are briefly reported which may be of some service to other workers.

The greater part of the technical work here described was carried out by Miss P. M. Waterworth. Her services and the equipment of the laboratory used were made available by the generosity of "Bundles for Britain," which organization provided a fund under the control of Mr. Rainsford Mowlem for laboratory work in connexion with his surgical unit.

Medical Memoranda

Reliability of the *X*-ray Diagnosis of Early Pulmonary Tuberculosis

The case cited by Dr. Sharpe in the *Journal* of Nov. 6, 1943 (p. 579) and the series of letters which followed have brought into prominence the important question as to how far *x*-ray films of the thorax can be relied upon in the early diagnosis of pulmonary tuberculosis. The following is a case in which a fatal miliary tuberculosis supervened shortly after the lungs were declared to be entirely free of evidence of infection by a reliable radiologist who has had great experience in reading radiographs. This *x*-ray examination was made while the patient was in hospital suffering from tuberculous meningitis.

An electric welder aged 21 was admitted to hospital complaining of severe headache. Clinical signs of meningitis developed, and laboratory findings confirmed the diagnosis. The radiograph of the chest taken while in hospital was negative. Death occurred on the thirteenth day after admission. Necropsy findings were: a typical Ghon lesion about 1 cm. in diameter lying immediately beneath the pleura in the upper part of the right lower lobe, the lesion involving a vessel of medium size; enlarged caseous glands at the root of the right lung; small caseous tubercles in the cerebral meninges, spleen, kidneys, and adrenals.

The questions which arise are how frequently cases are missed by the radiologist, and what type of lesion it is which fails to show up in the *x*-ray film. As to the first matter, Dr. Richards, radiologist to the Toronto General Hospital, has collected the statistics of active tuberculosis developing in enlisted men in Canada during the first two years of the war. He finds (*Amer. J. Roentgen.*, 1942, **47**, 66) that 16 men who had negative *x*-ray films on enlistment developed active tuberculosis—a percentage of only 0.004. We are informed verbally by a urologist in charge of one district in Canada, however, that he has seen no fewer than four cases of tuberculous epididymitis in soldiers who must have passed the test of a chest radiograph. This means that a percentage which is not negligible is declared free from evidence of pulmonary tuberculosis after inspection by the radiologist.

LESIONS WHICH FAIL TO SHOW UP

As to the matter of the type of lesion which fails to show up in the *x*-ray film, we are inclined to believe that many localized cases of primary tuberculous infection are invisible in radiographs. For the sake of brevity we may refer to this primary tuberculous pulmonary lesion as the Ghon lesion. It is situated at the periphery of the lung immediately under the pleura, usually not at the apex, and it consists of a small area of caseous consolidation later surrounded by a rampart of fibrous tissue. Spreading from it is a chain of infected lymphatics terminating in a caseous gland in the hilum of the lung. It is a moot point whether this lesion—which is usually small, often less than 1 cm. in diameter—can be demonstrated by *x* rays, especially if it be placed laterally and so hidden behind the ribs. When it becomes the seat of calcareous deposit it is more easily seen.

As to the matter of appearances in *x*-ray films which are suggestive of tuberculosis but which are not tuberculous in origin, probably every radiologist has seen suspicious lesions which disappear after a short time. Virus pneumonia of an

interstitial type and the rare condition of sarcoidosis both give pictures which may be confused with those found in tubercle.

The time which elapses between the exposure of susceptible persons to an open case of tuberculosis and the first radiological evidence of tuberculous disease is frequently three years or more in adults. This is the period of the Ghon lesion. During this interval the earliest evidence that a tuberculous focus is present in the body is the change in the allergic response to tuberculin.

Another point of importance illustrated by the above case is that throughout the first few years of infection there is a tendency to bacillaemia, with resultant metastatic foci in various organs such as meninges, bone, kidney, and epididymis. It is remarkable how often necropsies are performed on cases of miliary tuberculosis without the pathologist being able to assign to one particular lesion the role of primary focus of infection, the fact being that it is a minute primary focus of the type indicated.

We are inclined to agree with Dr. Fawcitt (*Journal*, 1943, **2**, 692) that there is no such thing as *x*-ray *diagnosis* but there is *x*-ray *evidence*, and that this fact is not yet fully appreciated. Nevertheless, mass radiography of recruits, schools, and nursing personnel is wonderfully reliable in spite of the occasional false negative and false positive.

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Tuberculin Jelly Patch Test

Other Tuberculin Skin Tests.—Since the introduction of the Vollmer patch test in 1937 much experience of its advantages and disadvantages has been gained. On the whole, it is a satisfactory and comparatively simple method of performing a tuberculin skin test. There is a tendency, however, for the patches to become dry and the tuberculin inactive, with consequent inaccuracies in the results. This has been especially noticeable during the war years. Compared to the Mantoux intracutaneous test, it can be said that the Vollmer patch test with freshly prepared patches is at least 95% accurate.

Tuberculin Jelly.—Recently an opportunity has arisen for the carrying out of a series of tests with tuberculin jelly, prepared as follows:

Old tuberculin (tuberculinum pristinum)	95%
Inert adhesive	5%

Method of Application.—The jelly is put up in small tubes, and after an area of skin between the shoulder blades has been carefully cleaned with acetone (for preference) a small portion of the jelly is pressed out on to the cleaned area. (I have found it more satisfactory to use a specific marking, which in my case has been the letter "V.") Without waiting for the jelly to dry, a piece of elastoplast about 1 in. wide and 2 in. long is used to cover the jelly and is allowed to remain on the back for the usual 48 hours. Meantime instructions are given that the child should not be bathed for this period, and after the removal of the plaster the back is viewed daily for several days.

Reading the Test.—A positive test is shown by an erythema or slight vesiculation of the skin in the shape of the marking used. A negative result is shown by a completely normal appearance of the skin area on which the jelly was applied.

Results.—Experience has shown that with the letter "V," the arms of which are 1/2 in. long, the reaction is equivalent to that of 0.1 c.cm. 1/100 old tuberculin (intracutaneous Mantoux test). In a recent series of 100 (specially selected) children, to whose backs the tuberculin jelly was applied, both at the Hospital for Sick Children, Great Ormond Street, and the Children's Department, Westminster Hospital, in-patients and out-patients, the following results were obtained:

Result	Vollmer Patch	Mantoux	Tuberculin Jelly
Positive ..	32	35	35
Negative ..	68	65	65
	100	100	100

Conclusions.—It would appear that in this series tuberculin jelly was a more accurate method of performing the skin test than the Vollmer patch test. No local reactions of undue severity were recorded. Other advantages appear to be: (1) the much smaller cost of the jelly in comparison with the patches, which is a considerable item in out-patient departments and clinic work; (2) the jelly will keep indefinitely in the tubes and is therefore more suitable for the general practitioner who may use this test only at infrequent intervals.

I have to thank Mr. Dreebin, of Messrs. Allen and Hanburys Ltd., for supplying me with the jelly and for his helpful suggestions.

London. DONALD PATERSON, M.D., F.R.C.P.

Reviews

AN ORNITHOLOGIST ON EVOLUTION

Systematics and the Origin of Species from the Viewpoint of a Zoologist. By Ernst Mayr. (Pp. 334. 26s. 6d.). New York: Columbia University Press; London: Oxford University Press.

Darwin had a profound knowledge of systematics, palaeontology, and genetics, on all of which the theory of evolution rests. His successors cannot hope to cover so wide a field, though Dr. Huxley has very nearly succeeded in his recent *Evolution*. Dr. Mayr is an ornithologist, whose work has been largely in the present Pacific war zone, and his facts, like those of Wallace, are mainly drawn from the study of living animals and their geographical distribution. The book is absolutely first rate, and every naturalist will find much in it to interest him.

After a very full discussion of geographical variation, the author concludes that some geographical races may develop into species, though he cannot agree with Darwin that "varieties are incipient species," since very few are likely to reach specific rank. The essential step in species formation is the prevention of crossing between two races. Dr. Mayr believes that, in animals at least, this almost always occurs in the first instance through geographical isolation. This may cause such differences of behaviour that the new species will not mate when they get the chance, and simultaneously or later, physiological differences which render the hybrids inviable or sterile. Here he will not convince all readers, though he makes a strong case.

Medical readers will be interested to see that he divides the malaria mosquito *Anopheles maculipennis* without hesitation into six species, which are reproductively isolated from one another, and does not regard them as mere "biological races," even though the adult forms cannot as yet always be distinguished. The student of *Homo sapiens* in his and her infinite diversity will find Mayr's discussion of other "polytypic species," all of whose geographical races can breed together, of great interest. It would have been a wholesome discipline if Hitler on the one hand and some of the more extreme exponents of human equality on the other had been compelled to study the geographical races of some of the birds of New Guinea in order to obtain a biological background for their theories.

While Dr. Mayr's book is not for general consumption, it should be within reach of every student and practitioner of medicine who wishes to keep up with the present position of evolutionary theory on the one hand and zoological classification on the other, as well as every ornithologist. To the student of genetics it presents a vast array of problems, of which the simplest is to determine, for every geographical race described, how far its characters are due to heredity, and how far to environment. I for one am going to re-read it several times.

J. B. S. HALDANE.

VASCULAR LESIONS AND TUMOURS OF THE SPINAL CORD

Vascular Abnormalities and Tumours of the Spinal Cord and its Membranes. By Roger Wyburn-Mason, M.D., B.Chir., M.R.C.P. (Pp. 196. 18s.) London: Henry Kimpton. 1943.

The relative rarity of the pathological lesions with which this volume is concerned must be largely responsible for their comparative neglect. Dr. Wyburn-Mason has been fortunate in having access both to the collection at the National Hospital and to cases coming under the care of neurosurgeons at several other centres. He has given a full, careful, and interesting presentation of his gleanings, which comprise 67 well-illustrated cases. This series represents a substantial addition to the literature, which so far contains little more than twice that number of cases. It will be profitably studied by those who are interested in these lesions, whether from the clinical or from the pathological aspect. The classification follows much the same lines as those previously outlined by Bailey and Cushing, and by Bergstrand. From the last-named, however, he differs in requiring a separate class for arterial anomalies and in including the cavernous angiomata with the telangiectases,

which are held—very credibly—to be precursors of the cavernous lesions. Bergstrand, it may be recalled, doubts the existence of racemose angiomata of purely arterial character. Wyburn-Mason, under the heading of arterial anomalies, describes aneurysms of the spinal arteries in association with coarctation of the aorta, and, further, anomalies associated with, or independent of, cardiac lesions. The latter are, however, unconvincing in the absence of histological verification.

The classification is marred by the inclusion of two dubious conditions—syphilitic aneurysm of the spinal arteries, and lymphangioma. Since these find no place in the author's extensive experience, and, moreover, are based on unsound pathological premisses, they would occupy a better perspective as footnotes than as chapter headings. It is surprising to read, on page 47, that attention is here being drawn to a clinical condition not previously mentioned in the literature—namely, spontaneous subarachnoid haemorrhage. This can hardly be what the author intended to convey, in view of his references to the literature in later paragraphs. His account of the symptomatology of this condition agrees well with that of Gowers.

The style and price of this volume are an agreeable surprise in a wartime production.

LABORATORY TECHNIQUE IN TYPHUS

Técnicas de Laboratorio en el Tifus Exantematico. By Prof. G. Clavero del Campo (Director del Instituto Nacional de Sanidad) and Dr. F. Perez Gallardo (Médico de Sanidad Nacional). (Pp. 185; with 104 figures, 7 coloured.) Madrid: Imprenta de Presna Española. 1943.

This interesting monograph was published as a sequel to the typhus epidemic which occurred in Spain during 1941–2. In an earlier volume by the same authors, which was also issued by the Spanish Health Directorate, an equally comprehensive review of the aetiology, clinical aspects, and prophylaxis of louse-borne typhus had been given. About half the present volume is occupied by the description of methods of isolating *Rickettsia prowazeki* by guinea-pig inoculation, by anal inoculation of lice, and by culture in the yolk-sac of the developing chick, and a further section deals with the isolation of the rickettsiae of murine typhus. There is a section on the Weil-Felix reaction, on agglutination with suspensions of rickettsiae, and on Giroud's intradermal test. In the remaining chapters the authors describe the preparation of the different types of killed typhus vaccine—namely, those made from rickettsiae grown in the louse-gut (Weigl), yolk-sac (Cox), rat-lung (Castaneda), and rabbit-lung (Durand and Giroud). Every detail of the various procedures described is fully illustrated by photographs and drawings, and readers with little knowledge of Spanish will find it comparatively easy to follow the text, thanks to the numerous and excellent illustrations.

In a foreword written by Prof. J. A. Palanca, Director-General of Public Health, an interesting account is given of the activities of the health department during the recent epidemic. This book should certainly be very helpful to laboratory workers who have had no previous experience of typhus but are likely to make contact with the disease during or after the present war.

THE ARMY MEDICAL SERVICES

R.A.M.C. By Anthony Cotterell. (Pp. 116; illustrated. 6s.) London: Hutchinson and Co.

In *R.A.M.C.* Anthony Cotterell gives a vivid picture of the many-sided activities of the Army Medical Services. In his own words, "the main purpose was to describe a difficult job well done by all ranks in the R.A.M.C., from the generals who advise and plan down to the orderlies washing out the medicine bottles." His description might itself be described as a difficult job well done, for it is a most readable book. A large part is made up of actual experiences in the field, and the author has chosen his material well and is an excellent story-teller. It is natural perhaps that the treatment and evacuation of battle casualties should have the lion's share at the expense of other interesting features, but Mr. Cotterell has managed to cover a very wide field. The problems of malaria control, water supplies, camp hygiene, preventive inoculation, blood transfusion, methods of dealing with psychiatric casualties, the "lead-swinger," and many other special aspects are faithfully dealt with and fitted into their place in the general plan. One would have liked to see a section on the Q.A.I.M.N.S., but it is good to note the author's promise that the sisters are to have a volume of their own.

The doctor or medical officer reading this book may at times be irritated by paragraphs reminiscent of the style of *First Aid to the Injured* or *R.A.M.C. Training*, or, in the section on oral hygiene, of a Health Week leaflet, but it must be borne in mind that these explanations are interesting and helpful to others. The gratitude of N.C.O.s and men of the R.A.M.C. is due to Mr. Cotterell for showing that they share in full measure the hazards and hardships of war with their comrades in the more spectacular branches of the Services, and that they are no less entitled to be called soldiers though nominally protected by the Geneva Convention. If it helps to remove the impression, unhappily prevalent in some quarters and keenly felt by many a humble private, that every nursing orderly is "either a conchie or a crock," this book will do a great deal of good.

Notes on Books

A Sixth Supplement to the *British Pharmaceutical Codex*, 1934, is published at 2s. 6d. by the Pharmaceutical Press, 17, Bloomsbury Square, W.C.1, by direction of the Council of the Pharmaceutical Society of Great Britain. It contains additions and amendments to the monographs in Part I and Part II, with amendments to formulae in Part III.

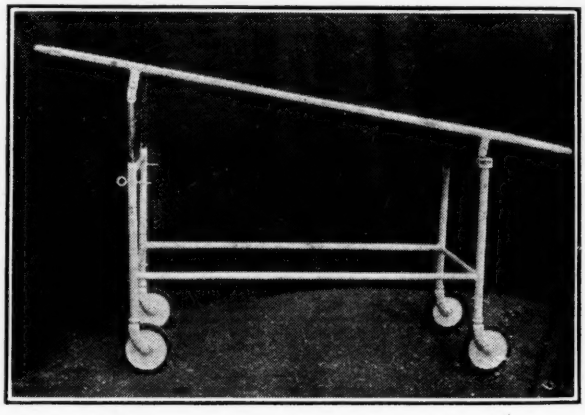
The County Accountants' Society (County Hall, Chichester) has published a booklet on *Classification of Patients under the Emergency Hospital Scheme*, prepared by the county accountant of Middlesex. It is believed that Mr. Rothwell's summary, which contains in handy form a complete classification of patients under the scheme, and gives useful information under each classification, will be of value to administrative and financial officers concerned with the scheme. The booklet has been nominally priced at 2s. 6d.

Preparations and Appliances

MODIFIED TROLLEY TO MAINTAIN TILTING DURING TRANSPORT AFTER SPINAL ANAESTHESIA

Mr. T. B. MOUAT, F.R.C.S., surgeon, E.M.S., writes from Wharncliffe Emergency Hospital, Sheffield:

After operation with light spinal anaesthesia, or in a shocked patient, transportation back to the ward in a safe head-down position is facilitated by a simple modification of the ordinary type of theatre trolley.



The two tubular supporting pillars at one end have been cut across at their upper ends and two slightly smaller tubes, which are hinged at their attachments to the under-surface of the table, are telescoped into the original table supports, where they are fixed, to maintain the desired tilt, by pins in holes bored through both tubes. The attachments of the pair of supporting pillars under the opposite end of the trolley must, of course, also be hinged to allow the top of the trolley to be tilted in this way.

Our thanks are due to Mr. Sidney Wright of the hospital workshop for his co-operation in carrying out the alteration.

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TREATMENT WITH PENICILLIN

The therapeutic properties of penicillin were first disclosed in animal experiments by Florey and his co-workers[1] in 1940, and their first account[2] of succeeding essays in the clinical field appeared in the following year. These were the days when penicillin was being made only in the laboratory, and supplies sufficed for the treatment of only 5 cases of severe staphylococcal infection and a few of conjunctivitis and other local infections. The next report from Oxford,[3] nearly two years later—an interval during which both production and the quality of the product had been improved—added a further series of cases of staphylococcal septicaemia, osteomyelitis, and cavernous sinus thrombosis, all successfully treated, many cases of chronic sepsis treated locally, and further information about eye infections and the treatment of mastoiditis. These studies laid the foundations of penicillin treatment, and clearly indicated two things: that given systemically the drug will control septicaemia or other extensive and dangerous infections due to *Staph. aureus*, and that applied locally it is the perfect antiseptic when circumstances permit its continuous action. It should not be supposed that staphylococcal infections stand alone in being thus amenable to systemic treatment; they were chosen because the sulphonamides have so little real power over them. Haemolytic streptococci and pneumococci are even more susceptible to penicillin, but the infections which they cause are usually so relatively controllable by sulphonamide treatment that the use of penicillin for them was unjustified. From this point the story is taken up elsewhere than in Oxford, and several further specific uses for penicillin have been described in later papers. These include the treatment of burns, which has been studied by Bodenham[4] and by Clark *et al.*[5]; of septic infections of the hand, where according to Mrs. Florey and Williams[6] a small amount of penicillin will go a long way in preserving function and restoring it rapidly; and the treatment of battle wounds, recently reported on by Florey and Cairns.[7] These are the efforts of our own workers. Clinical study on an even larger scale has been in progress in the U.S.A., and we referred not long ago[8] to a preliminary report on the treatment of no fewer than 500 cases, many of which received systemic treatment; but details of many of the groups of cases included in this total have not yet been published. Much larger supplies of penicillin are available in America, and it is there that the treatment of both gonorrhoea and syphilis has been developed, as we noted in a recent issue.

1 *Lancet*, 1940, **2**, 226.
2 Ibid., 1941, **2**, 177.
3 Ibid., 1943, **1**, 387.
4 Ibid., 1943, **2**, 725.
5 Ibid., 1943, **1**, 605.
6 Ibid., 1944, **1**, 73.
7 *British Medical Journal*, 1943, **2**, 755.
8 Ibid., 1943, **2**, 582.

A year ago, when supplies from commercial sources in England had reached sufficient proportions, some was placed at the disposal of the Medical Research Council, and through its Penicillin Clinical Trials Committee several centres were established for further therapeutic study. A report from one of these centres, taking the form of eight separate papers on different aspects of the subject, occupies the whole of the space devoted to original papers in this issue of the *Journal*. In their introduction Christie and Garrod define the policy of such a centre, and refer to the transition from all-embracing enthusiasm to caution in selecting cases with particular ends clearly in view, which is inevitable when supplies are limited. There is still not nearly enough penicillin available for treating all the cases even of a few conditions, such as staphylococcal septicaemia, in which the value of heavy systemic dosage is fully established. Since the purpose of the work was to break new ground rather than to exploit existing knowledge, such cases had often to be refused. It is nevertheless as well to warn those who will have greater opportunities in the future that even penicillin is no guarantee of cure in staphylococcal septicaemia. Apart from several cases of osteomyelitis in this series with a positive blood culture, all of which did well, there were 4 cases of septicaemia in which 2 patients died in spite of heavy and long-sustained dosage. The opportunity afforded by these and other cases undergoing systemic treatment was taken to study new methods of administration. Florey advocated originally a continuous intravenous drip and later single intramuscular injections at 3-hourly intervals. The disadvantages of the former are difficulty of accurate regulation, liability to thrombosis, and sometimes shortage of veins; of the latter, the ordeal for the patient who must submit to painful injections continued with inexorable regularity by night as well as by day for perhaps more than a week. The merits of both routes seem to be combined in the intramuscular drip described by Morgan, Christie, and Roxburgh, and these authors have also explored the possibilities of infusion via the bone marrow.

A policy at this centre has been to study further the treatment of infections of bone, and two papers deal with this from different aspects. In Robertson's hands the treatment of acute osteomyelitis by the systemic route had the almost uniformly favourable results which have already been reported. Early treatment appears to be essential, the least satisfactory case being one in which it was resorted to a full month after the onset. The account of attempts to treat chronic bone infections, whether haematogenous or due to compound fractures, and whether by local application in various forms or even by the systemic route, makes very different reading. It is indeed a record largely of failure, and surgeons and others who are clamouring for penicillin in order to treat cases of this kind may console themselves with this evidence that their deprivation may not be the misfortune they think. Robertson himself gives good reasons for these disappointing results, and contemplates changes in surgical technique which may improve them. Penicillin is not a magic elixir the mere instillation of which into a sinus or bone cavity will lead to healing. It can deal only with bacteria

which it can reach, and it cannot remove dead or irreparably damaged tissue. These findings may usefully be compared with Mowlem's experience in the treatment of osteomyelitis of the mandible. His practice here is to remove all the affected bone, leaving perhaps only a thin lingual plate to maintain continuity. It was formerly necessary to leave the wound open and allow it to granulate. He now closes it completely, having inserted two tubes through which the bone cavity can be filled with penicillin solution from above; infection is thus suppressed and rapid healing is secured. This is a new application of the principle first enunciated by the Floreys, with the new mastoid technique as their example, that septic wounds which are to be treated with penicillin must be sewn up in order to retain the solution. The success of the operation is clearly the effect of radical removal of affected bone, and perhaps nothing short of this will provide the answer to chronic osteomyelitis in other parts of the skeleton. The mandible has two advantages from this point of view: it is easily accessible and non-weight-bearing. Corresponding treatment of some of the long bones may well be surgically impossible.

Several papers deal wholly or in part with various infections of soft tissues. Fraser has begun a study of the treatment with penicillin of staphylococcal breast abscess, and it seems that aspiration of pus and injection of penicillin solution will sometimes replace operation, and usually hasten recovery. It has yet to be decided whether, as is hinted elsewhere in connexion with empyema, it may prove better policy to evacuate the contents of the abscess surgically and rely on penicillin to achieve and maintain subsequent sterility. Barron and Mansfield bring out several useful points in connexion with the use of penicillin in plastic surgery: it has evidently several uses here, as would be expected from the damaging part which pyogenic infection can play, and the usual full accessibility of the infection to treatment. Roxburgh, Christie, and Roxburgh describe the treatment of 75 cases of various diseases of the skin. This is almost a new field and evidently a promising one, at least in so far as the condition treated is due to infection by staphylococci or streptococci. That impetigo should be curable is no new thing, but penicillin seems to achieve this effect more quickly than anything else. That sycosis should be quickly controlled in a majority of cases is decidedly something new, and this achievement, should longer experience confirm it, will rank high among the minor benefits of the discovery of penicillin.

A final paper by Garrod gives an account of the extensive laboratory work entailed by fully controlled penicillin treatment. The necessity for this may well give pause to those who look forward to the wider availability of penicillin, since laboratory service on this scale is not everywhere available; but perhaps greater experience and more standardized methods of treatment may dispense with the need for at least some of this work. New observations reported are the variable sensitivity to penicillin of *Actinomyces*, with corresponding variations in the effects of treating several cases, and the susceptibility to penicillin of mouth bacteria generally, again reflected in the good results in osteomyelitis of the jaw, a condition of which the flora, aerobic and anaerobic, may be complex. Actual instructions for the performance of laboratory investigations in connexion with penicillin treatment are not given; for these the reader is referred to M.R.C. War Memorandum No. 12, the publication of which we noted last week.

We look forward to hearing further accounts of the work on this subject now in progress. The general principles are now understood, but specific new applications continue to be discovered. This is not merely a matter of thinking of something new to treat: it may involve devising a new method of application or a change of surgical technique to suit the altered circumstances created by penicillin. There is thus still room for enterprise, notably in special departments of surgery which so far have had little chance to try their hand with the new weapon.

CUTANEOUS DIPHTHERIA

Diphtheria in cutaneous and other forms gave a lot of trouble to the Army in the Middle East during the war of 1914–18, and it is once more giving concern to medical officers on service. Major Bensted[1] described what was probably the first epidemic of faucial and cutaneous diphtheria among troops on a military frontier: the epidemic was brought under control by Schick-testing and active immunization. Cameron,[2] Muir,[3] and Marshall[4] describe outbreaks in Northern Palestine and in the Middle East in 1940 and 1941. Cameron tells of the Jewish children in Palestine near the camps with a considerable incidence of nasal, crusted, discharging sores, and refers to a local description by Bernfeld.[5] Lack of full laboratory facilities prevented the complete examination of strains of diphtheria-like bacilli found in the children or in military patients, but of the 40 cultures obtained from clinically accepted cases of diphtheria, 31 strains proved virulent on test. Some were reported avirulent, but the author points out that the suspension for animal tests was made in saline—a fluid noxious to diphtheria bacilli.[6] Cameron discusses whether contact with horses might account for infection, but he failed to find bacilli in the throat, nose, or skin of horses or in the fodder. Parish and Okell[7] found virulent *C. diphtheriae* in three of 13 swabs taken by Dalling from wounds in horses occurring in a military camp in Scotland. Cameron and Muir[3] treated their epidemic of cutaneous diphtheria by isolation, Schick-testing, and active immunization. Their observations agree in all important points with those of Bensted and the American Official History of the War.[8] Cutaneous diphtheria may complicate any form of wound, burn, blister, impetigo, eczema, Oriental sore, whenever faucial diphtheria prevails and the patient may infect his own skin. As skin lesions have been followed by severe paralysis, it is wise to give such patients

1 *J. R.A.M.C.*, 1936, **67**, 295.
2 *Edinb. med. J.*, 1943, **50**, 1.
3 *Lancet*, 1942, **2**, 720.
4 *Med. J. Austral.*, 1942, **2**, 14.
5 *Fol. otolaryng. orient.*, 1935, **2**, 154.
6 *J. Path. Bact.*, 1940, **51**, 287.
7 *Brit. J. exp. Path.*, 1926, **7**, 173.
8 *U.S. History of the World War*, 1928, **9**, 259, Washington.

an immediate and substantial dose of antitoxin—e.g., 15,000 units. Swabbing of contacts, Schick-testing, and active immunization have, even under war conditions, given a rapid and satisfactory control of epidemics.

When the local lesion comes under medical care the crusts may be removed by saline packs or baths or with glycerin magnesium sulphate or hydrogen peroxide, revealing an ulcer with greyish, membranous slough. Dressings cut to fit accurately in the wound are valuable; hairs around the edge are removed and the skin protected from further infection. The rapidly forming granulations are carefully protected; scarlet red ointment and the aniline dyes have been much used. (Harries[9] gives a valuable review of cutaneous diphtheria.) Carrier rates of from 4 to 9% were observed by Cameron. The few persistent carriers were cured by tonsillectomy. H. Williams[10] recently described an unusual series of cases. Over a period of eight months 19 patients in a military hospital yielded positive cultures a few days or weeks after admission and were found to be suffering from diphtheria of the skin or eye. Six had conjunctival infections, and one patient suffered grave damage to both eyes. The 19 patients were transferred to the isolation hospital; all received antitoxin, and fortunately no paralysis developed. During the same period 17 cases of faucial diphtheria and one of diphtheritic rhinitis, including seven of the staff, came from the same military hospital. Williams suggests the need for more frequent bacteriological investigations of skin infections. Cameron and Marshall both stress the need for active immunization of troops in the Middle East. This plea comes also from Wheeler and Morton,[11] who describe a severe epidemic at Halifax in Canada. The diphtheria occurred there at much later ages than usual; in females the greatest incidence was in the 20–25 age group. The Halifax epidemic was presumably maintained "by the exchange of infection between the soldiers, sailors, and visitors and their wives or sweethearts in the town."

It is not easy to see clearly the relationship between McLeod's types of diphtheria bacilli and the distribution of the disease. The Halifax outbreak was thought to be the first on the West side of the Atlantic due almost entirely to the gravis type. Murray[12] records a curious position on Witwatersrand in South Africa. Intermedius strains were never recovered from local cases of diphtheria; about 85% of local infections were due to mitis, and the case mortality was high—about 9%. Murray believes that with a high Schick-positive rate in the community and a low carrier rate among children the stage is set for an explosive outbreak at any time from the importation of a more virulent strain; he concludes that active immunization is urgently necessary. Since in certain districts the predominant type may alter from year to year and even from season to season, we obviously have still much to learn. The artificial immunization of some three millions or more of children in England during the past few years may result in disturbance of type distribution or even in the prevalence of types difficult to classify.

[9] Hurst, *Medical Diseases of the War*, 1943, chap. 25, London.
[10] *British Medical Journal*, 1943, **2**, 416.
[11] *Amer. J. publ. Hlth.*, 1942, **32**, 947.
[12] *S. Afr. med. J.*, 1942, **16**, 247.

CARE OF THE PREMATURE INFANT

One important way in which neonatal mortality can be reduced is undoubtedly by better facilities for the care of the premature infant. It is estimated that about half the deaths in the first month of life occur in the prematurely born, and experience has shown that organized effort can do much to improve the chances of the immature infant. The often-quoted Chicago figures bear this out, for coincident with a reduction in the neonatal death rate in that city from 37 per thousand live births in 1925 to 18 in 1940 there was developed a city-wide plan for dealing with the premature infant. In this country a start can be fixed in the year 1937, when a joint committee of the Royal College of Physicians of London and the Royal College of Obstetricians and Gynaecologists put forward a recommendation that the "5½ lb. or less" standard should be accepted as a working definition of a premature or immature baby "for the purposes of comparison of records." The next landmark is in the issue of a circular by the Ministry of Health to all welfare authorities, dated March 22, 1944, on the care of premature infants. This is based upon the recommendations of the Minister's Advisory Committee on the Welfare of Mothers and Young Children, and while it is quite clear that many of the suggestions cannot be put into effect at the present time because they involve staff and accommodation they give local authorities a clear lead in their planning for the future. First comes the "provision of accurate information"—namely, a means of securing notification by the simple device of having the weight of all newborn infants noted on the notification of births card when this is 5½ lb. or less. For the baby to be looked after in its own home importance is attached to certain details of accommodation, equipment, and expert services. A list of special equipment, to be lent by the authority when necessary, includes draught-proof cots, suitable clothing, hot-water bottles, electric blanket pads, special feeding-bottles, thermometer, and mucus catheters. A supply of expressed breast milk is also recommended when this is necessary. Specially trained midwives or health visitors are mentioned, and the services of a paediatrician are to be available. Home helps also come into the scheme. For immature babies born in hospital or admitted because of the need for institutional care the circular enters into important details as regards accommodation. Warm rooms with "cooling-off" facilities and regulated humidity receive recognition, and details of nursing staff are set out with the object of securing skilled care and continuity among the senior staff. A paediatrician is to be attached to all maternity units and his services made available for all special units for premature babies, a reform for which both obstetricians and paediatricians have been pressing. A special form of transport is mentioned, and the circular concludes with an important reference to the follow-up of infants "immediately" on discharge from hospital to their own homes. Action on the lines of the circular is long overdue, and it is to be hoped that authorities will lose no time in putting into effect as much as is practicable now.

WARRINGTON YORKE MEMORIAL FUND

The late Prof. Warrington Yorke was a product of the Liverpool School of Tropical Medicine, and one of its most distinguished members. In addition to his jealous maintenance of the high standards set by earlier workers at the school he earned for himself an international reputation in the world of medical science, and his outstanding original work on trypanosomiasis, blackwater fever, the nematode parasites, and many other parasitic and tropical diseases has permanently enriched our knowledge of these

subjects. In the latter part of his career, so untimely cut short, Yorke turned his exceptional energy and ability more and more to the elucidation of the mode of action and the therapeutic value of chemical compounds, especially in parasitic diseases. As a direct outcome of his pioneer work new potent weapons were forged against a number of diseases, in particular leishmaniasis and trypanosomiasis. These discoveries were of far more than academic interest; indeed, it may be said that Yorke's introduction of drugs of the diamidine series is making it possible to master kala-azar in those parts of the world where the disease is peculiarly resistant to the antimonial compounds. Just before he died he had initiated further studies in chemotherapy, and it was his aim to promote chemotherapeutic research in Great Britain to the front rank and firmly to establish Liverpool as one of its leading centres. To that end he laid a solid foundation on which to build.

The Council of the Liverpool School of Tropical Medicine feels that a fitting memorial to this remarkable man would be to place on a firm financial basis the recently created Chemotherapeutic Research Department, where the work he inaugurated will be continued in association with his name. To this end a Warrington Yorke Memorial Fund has been opened, and the Council believes that Yorke's many colleagues, friends, past students, and others who have benefited by the great advances which he helped to make in tropical medicine and hygiene during his forty years of service, will wish to be associated with this memorial. The Council of the School would welcome subscriptions, however small, which should be addressed to: The Honorary Treasurer, Liverpool School of Tropical Medicine, Chamber of Commerce, 1, Old Hall Street, Liverpool.

SURGICAL SERVICE FOR INDUSTRY

The Birmingham Accident Hospital has completed its third year. It was a pioneer effort, at least on such a scale, and it has attracted observers from various parts of the country whose institutions have wished to profit from the Birmingham experience. Last year the number of new in-patients was over 2,000, and the number of day-ward cases 2,500. These latter are patients admitted to a ward for less than twenty-four hours, but requiring an anaesthetic, an operation, and a recovery period in bed. We can well believe that the short-stay ward is the busiest and the most expensive in such a hospital. In addition there were some 18,700 new out-patients, and nearly 3,000 new patients treated in the rehabilitation department. Altogether the total daily attendances number something like 400—an indication of the frequency of accidents, mostly minor no doubt, in modern high-pressure industry. The work of the out-patient departments is divided into three groups: fractures and the more serious types of injury; injuries without bone damage but including infections; and, finally, rehabilitation. For each of these groups there is an appointments system, so that waiting-time, especially to be avoided in an industrial hospital in war, has been greatly cut down. The complaint, however, is of shortage of medical staff. The medical staff numbers only ten, with three consultants. It is hoped that when the new out-patient department now being constructed is ready and equipped with new facilities it will be appreciated that the allotment of more medical staff to an institution of this kind would mean, among other things, economy of medical man-power.

One-sixth of the total floor space at Bath Row is devoted to special departments concerned with rehabilitation, meaning physiotherapy, physical training, and occupational therapy; and in all these the surgeons who have been engaged from the first in the treatment of the particular case are present to supervise these later phases of recovery. Not everyone appreciates how individual a thing is restoration to fitness. This work does not lend itself to the construction of precise schedules. One man's corrective is another man's setback. The work calls for great adaptability on the part of the surgeon, of those who carry out his instructions, and of the patient himself. In industrial accidents rehabilitation and treatment are intertwined. They begin together on the day of the injury, and treatment ends with rehabilitation when the man is restored so far as possible to industrial and social capacity. Moreover, rehabilitation includes more than getting an injured limb back to full function. There may have been a more serious disturbance in the patient's social background, and, however effective the games instructor and the occupational therapist may be, they cannot achieve full restoration so long as the man is fretting over his domestic and economic problems. Therefore the social service department is as important as any in a rehabilitation centre.

Another participant in the work is the industrialist. An experiment has been undertaken by the Birmingham Accident Hospital in conjunction with the Austin Motor Company in which the firm has fitted up a workshop at its factory, under the supervision of the works medical officer, for the employment of disabled workmen. When the treatment of the men in hospital has reached a certain stage of recovery the rehabilitation methods can be stepped up to production level, using the same machines as in the factory, perhaps with some adaptations, and the man begins to feel that instead of playing at industry he is again a unit in the industrial organization. Up to the end of last year about 150 disabled persons returned to normal employment after passing through this special workshop. The scheme of a rehabilitation workshop attached directly to industry and at the same time closely co-operating with the hospital has been a success, and it is hoped that with the co-operation of other Birmingham industrialists it may be extended. The subscriptions to the hospital from industry during the year amounted to just upon £18,000; the City of Birmingham gave £10,000; and contributions on account of services amounted to £11,500 from the Hospitals Contributory Association and some £12,800 from the Ministry of Health; but there is an excess of ordinary expenditure over ordinary income of £4,000.

An industrial hospital offers fresh fields for research. The Medical Research Council has acknowledged this by establishing two research units in Birmingham. One of these is concerned with burns and is under the care of Col. Leonard Colebrook (whose letter in the *Journal* of March 4, page 342, on the first-aid treatment of thermal burns and scalds will be fresh in the minds of readers). The other unit, under Prof. A. A. Miles, is concerned with the bacteriological side of wound infection in industry. This unit has studied during the year over 5,000 swabs from more than 1,000 wounds, and on the basis of the survey, and with the co-operation of the hospital clinical and nursing staff, a new technique of wound dressings has been instituted. An eight-months research on the use of penicillin in the healing of wounds and various septic conditions has been completed during the year by Dr. Ethel Florey, and it is mentioned that about 1,000 man-days were saved by the treatment of 35 industrial cases with this preparation. But penicillin is not yet available in sufficient supply to be used in the hospital. The arrangement of these researches is another example of the enterprise shown in this field, and there is every advantage to be gained from a study of such problems on the spot—that is to say, in a hospital which keeps an open door for the daily victims of the industrial machine.

Correspondence

Reform in Medical Education

SIR,—Dr. Douglas Guthrie (March 25, p. 432) is right that the principle which is fated to co-ordinate our ever-multiplying medical specialisms need not be sought in modern psychology. Speaking generally, this latest "subject" (which emanated originally from the decadent great-city life of Greater Germany) is itself but another specialism, isolating a "psyche" from the rest of life. How then, asks Dr. Guthrie, are we ever to supply medical students with the first principles of the healing art? He thinks, by teaching them the history of medicine. I should greatly doubt, however, whether this will prove a solution, and, apropos, may I touch on some personal experience? Before the last war, being in general practice in Edinburgh, I devoted a lot of my spare time to a survey of the whole field of medical history, and even gave lectures on the subject. Incidentally I translated for the Loeb Classical Library one of Galen's most characteristic shorter treatises, and became very familiar not only with the vocabulary but with the outlook of this greatest synthetic medical mind of antiquity. I cannot speak too highly of the stimulating effect which this study and discipline, being grafted on my own daily experience of practice, had on my own mind, and how it deepened my appreciation of and love for the *ars medendi*. But I firmly believe that the average medical student of to-day would, by reason of his preliminary training, be incapable of profiting by lectures on this topic. To the large majority of these young men it would just prove another "extra subject" to be memorized along with all the other "facts" of an already grossly overloaded curriculum, thus fragmenting their minds more than ever. Only experience of general practice, and preferably of country practice, where the doctor is still thrown much more on his own responsibility than in the cities, can breed a mind capable of absorbing and profiting by the cultural side of medical humanism.

If the powers that be, including the framers of the present White Paper, were really, in the main, concerned with the health of our people and not, in the main, as they are, with making the world safe for bureaucracy, I would even now ask a favour of them. I would ask them to confine their legislative zeal to two enactments—one privative and the other constructive. From the National Health Insurance system I would ask them to cut out, by force if necessary, at least another 50% of this certificate-signing business which is now driving so many members of our profession desperate, if not melancholy mad. And the positive measure would be to make every young graduate begin his professional career by serving as an apprentice for two or three years to an established country doctor. This would be by far the most practical way of ensuring that "return to Hippocrates," with its synthetic and practical aim, which Dr. Douglas Guthrie and others so properly desiderate. It would rear a race of doctors of whom many, I believe, would eventually become capable of profiting by a study of the history of medicine. Such, however, should not be lectured to overmuch. They would need only to have their attention directed to the valuable material available, when, I am convinced, they would grasp it with open arms. Also they would grasp it each in his own way—which, after all, is the best kind of individualism.—I am, etc.,

North Queensferry, Fife. A. J. BROCK.

Shock Treatment of Mental Disorder

SIR,—Dr. Kalinowsky's very wise letter on this subject (April 1, p. 453), and the previous correspondence, once again raise the primary issue—are there in fact any diseases of mind *qua* mind? Is mind, whatever and wherever it is, capable of disease? Or are the abnormalities of speech and behaviour, at present so often regarded as being evidences of purely mental disease, in fact due to structural or biochemical defects in the nervous system, including the brain? In other words, are they really dependent upon the condition of the cells, tissues, or secretions by which mind—under any hypothesis as to its nature and locality—can only, in this everyday world, feed and express itself?

In the absence, for instance, of post-mortem observations and a knowledge of the action of the responsible spirochaete, the speech and behaviour of a man suffering from cerebral syphilis might well seem—and did probably once seem—to be a purely mental disease, approachable only by psychological methods. But research has come to show that the anti-social behaviour, the grandiose ideas, the decaying standards of personal cleanliness, are in fact due to structural changes—to some extent curable or at least preventable by appropriate treatment of the invaded or threatened tissues. Other examples can be readily thought of.

May it not therefore be possible that the less gross aberrations of speech and behaviour associated with such conditions as schizophrenia, melancholia, hysteria, and the great group of anxiety and other neuroses are similarly due to structural or biochemical defects in nerve and brain tissue, relatively small perhaps and at any rate not yet discovered? We do not know the exact means whereby shock therapy can apparently transform and bring back to normal—at least for a time—aberrations of speech and behaviour. But it is difficult to believe that its action can be other than organic—an effect upon tissue and material processes.

To accept this view is not to decry the value of psychiatry, although it may challenge the foundations upon which some people base it. Thus A may have been bullied in youth, had dominating parents, and been shut up in a dark cupboard as a punishment. But he does not develop either an inferiority complex or claustrophobia. B, who has had the same experiences, does. The difference between them may still be explained by some relative defect in B of nerve or brain tissue or biochemical adjustment. But, pending the discovery of this, the psychiatrist can do a very great deal in providing B with a sane outlook on his handicap and a crutch to mitigate it. Just, however, as the anxiety and irritability so often associated with hyperthyroidism disappear after a successful thyroidectomy, so in future—if the possibility is acknowledged and sought for—may the anxiety neuroses and many other hitherto supposedly purely mental affections become removable by an appropriate treatment of material cells, tissues, or secretions.—I am, etc.,

London, E.C.1. H. H. BASHFORD.

*** But the problem remains—how does the psychiatrist provide "material cells, tissues, or secretions" with "a sane outlook"?—ED., *B.M.J.*

SIR,—In his recent letter from New York (April 1, p. 469) Dr. Kalinowsky, while agreeing that convulsion therapy promotes accessibility to later psychotherapy, still maintains that the latter is of secondary importance. From the purely utilitarian standpoint he is correct, though he himself expresses disappointment at the empiricism with which the treatment remains enshrouded. I write now to offer certain suggestions and to draw attention to certain facts which seem to throw light upon the *modus operandi* of electrical convulsion treatment (E.C.T.).

There are two facts which will be generally admitted by all exponents of the method: first, that some degree of amnesia is to be expected, at least for a time; secondly, that there is a tendency for the patient to relapse, a tendency seemingly inherent though not invariable. In the writer's opinion these two different tendencies are in a measure inversely related. Dr. Kalinowsky correctly stresses the more striking success of E.C.T. in the psychotics rather than the psychoneurotics, pointing out that it is precisely where psychotherapy is most applicable that E.C.T. relatively fails. Now, it is the degree of insight, or, in other words, of conscious inner perception, of the trouble which distinguishes the psychoneurotic from the psychotic patient. In short, the greater the degree of higher conscious perception the less is the response to E.C.T. Here we have an array of facts—which incidentally could be added to—which seemingly all point in one direction—namely, towards the view that the production of amnesia is closely related to the improvement which ensues. The degree of amnesia produced doubtless varies according to the degree of consciousness which pre-existed in the psychical system

concerned; in the lesser illuminated psychical systems where conflicts reside it may amount to a temporary total abolition. If this point of view is correct, it means that, while we are affording the patient great relief, we do so only by diminishing his field of consciousness.

I would suggest that it is because the amnesia is transitory that the patients tend to relapse and their repressed conflicts tend to return. All this carries the inevitable corollary that even the improvement in accessibility afore-mentioned is more apparent than real, since the deeper systems will have become even more inaccessible. This artificially produced accentuation of repression is diametrically opposed to the aim of psycho-analysis, which, of course, is concerned with the removal of conflict by the widening of consciousness.

If upon further investigation these findings and views are confirmed they will clearly preclude the hope that E.C.T. is a method ever likely to further scientific understanding of the mind and its processes. Nevertheless, I still hold the view that in E.C.T. we possess the most generally applicable, and therefore upon the whole the most valuable, method of treatment in vogue in psychiatry to-day.—I am, etc.,

Warlingham. WM. H. SHEPLEY.

Vaccination against Smallpox

SIR,—In the annotation on vaccination against smallpox (*Journal*, March 18, p. 399) it is stated that "ordinarily a single linear scratch one-quarter inch long is sufficient." In the recent epidemic in Edinburgh the officially issued instructions were: "The actual vaccination should consist of three parallel strokes 3/4 in. long and 1/4 in. apart." This reveals a very pronounced difference of opinion among authorities. I find that in Price's *Practice of Medicine* (4th ed., 1934) it is stated that "the degree of protection afforded against smallpox is in some degree proportional to the extent of the vaccinal lesion, and the resulting scars should, together, cover an area of not less than half a square inch. Hence the advice always to make at least two insertions and preferably four." In the 1942 epidemic in Glasgow the scarification officially prescribed was "three strokes 3/8 in. long and 1/8 in. apart."

In the above-mentioned annotation the writer, after saying "ordinarily a single linear scratch one-quarter inch long is sufficient," goes on to say that "in the presence of an outbreak of variola major three well-spaced incisions may be made to give a more solid immunity." It is difficult to follow his reasoning. Surely in any case—whether in the presence of an outbreak of variola major or not—the highest possible immunity should be one's aim.

After the lapse of more than 100 years since Jenner's discovery it seems strange that there should be no general agreement as to the best way of making the inoculation.—I am, etc.,

Tunbridge Wells. E. WEATHERHEAD.

*** The general decline in the acceptance of vaccination, the mild character of smallpox then prevalent in this country, and the occasional occurrence of post-vaccinal encephalitis led the Committee on Vaccination to issue an Order in 1929 directing public vaccinators to make a single linear insertion, which was calculated to protect against the less virulent virus and unlikely to be followed by untoward sequelae. In the presence of an outbreak of variola major, however, 2, 3, or 4 insertions are advisable in order to give a greater degree of immunity, for collected data about smallpox in vaccinated persons indicate that the degree of protection is proportionate to the area of scarring.—ED., *B.M.J.*

Vitamin D in Rheumatism

SIR,—Your annotation on the subject of vitamin D in rheumatism calls to mind a problem in the mechanism of that disease which caused me some difficulty at the time. I had formed a satisfactory hypothesis to account for the similarity between the agents which brought about temporary cure in leprosy—I was looking after some lepers at the time—and those used in rheumatism. This hypothesis was severely shaken by an account which reached me of the work of Dreyer and Reed with vitamin D in rheumatism (1935).

For those who are unfamiliar with the treatment of leprosy it is necessary to state that many agents which are known to cause a recession of skin lesions in leprosy are similar to, or identical with, those reported to cure rheumatism. As an example, intravenous T.A.B. vaccine has its advocates in both diseases. Sometimes a more severe shock—intravenous tinned milk, or dyestuffs of some kind, or a large quantity of sodium salicylate—is used in leprosy. Gold and sulphur injections are popular in the treatment of both diseases. Intercurrent acute infectious diseases have similar beneficial effects in both cases, typhoid and kala-azar, for example, in leprosy being equivalent to measles or acute hepatitis in rheumatism. In seeking for the mechanism of such cures the study of rheumatism, where clinical observation has been more extensive and more accurate, offered great promise.

The one factor which I found common to all the agents that cure rheumatism is that which I have labelled debility (1942). Whether it is induced by the accidental trauma of falling down and fracturing a femur or by the more deliberate and calculated procedure of "bone forage" does not seem to matter much, provided it is really severe. Whether a woman gets jaundiced or pregnant the beneficial effects on her rheumatism are the same. So far as his rheumatism is concerned it is a matter of indifference whether the patient suffers from gold poisoning with, say, 5% mortality, or atophan poisoning with 45% mortality; in both cases, whether he lives or dies, his rheumatic lesions fade. On the surgical side Leriche started with quite a plausible theory to justify parathyroidectomy and sympathetic ganglionectomy. But the theory was exploded by Simon and Weill, who got the same magical results from a mock parathyroidectomy.

It was becoming evident to me that in leprosy and in rheumatism if you knocked the patient about sufficiently you broke down his resistance—of which the lesion in either case is the anatomical expression—with at least temporary good results. On the medical side the more poisonous the drug the better the result, and by raising the dose it is possible to make the pharmacological properties of all drugs converge to a point where they repress the lesions of rheumatism or leprosy. The surgeon who finds, or imagines he finds, sufficient reason for a major operation to cut out the parathyroid, or pretend to cut it out, to excise the gall-bladder or uterus or other septic focus, to chisel away a piece of tibia, or to remove the lumbar sympathetic ganglia, appears to achieve really good results. But the operation must be a major one. Brutality, it seems, yields better dividends than sympathy and sanatorium regime in the treatment of rheumatism.

At this stage of my observations I was confronted with an account of the work of Dreyer and Reed with vitamin D in rheumatism. Here, it appeared, was the vitamin which controlled calcium metabolism being used to restore the diseased bone to a state of healthy resistance. This was rather disconcerting from my point of view. The report which I had read, like your own account, made no mention of dosage. Park (1938), reviewing the toxicity of vitamin D with special reference to its use in rheumatism, considers that 200,000 units daily is the maximum safe dosage. To achieve results in rheumatism, as I might have guessed, the dosage has to be pushed, in some cases, to 1,000,000 units a day.—I am, etc.,

Albury, Guildford. WILLIAM HUGHES.

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The "Extra Pharmacopoeia"

SIR,—I am sorry that Mr. Linstead finds it necessary to protest on behalf of the Pharmaceutical Society against my review of the latest edition of Vol. II of the *Extra Pharmacopoeia*. The most serious part of his letter is the suggestion that my duty was not done conscientiously, and that I deliberately looked for material to give spice to my criticism. Now, I have been using the *Extra Pharmacopoeia* as a book of reference quite regularly for the last seven years, and recommending it warmly to others. I may not know much about it, but that is not because I am unfamiliar with the book. If I boil down the main complaint of my review and put it forward in the most serious manner, I would say that the two volumes are largely spoilt by the inclusion of information of no interest or importance. This amounts to something like 60% of the

total information in the books. The presence of this matter greatly reduces the accessibility of the remaining 40%, which consists of first-rate material most carefully collected. Here again I would draw a distinction between analytical methods and information about new medicines. The former is very well done, while the latter is much less well done. I expect the main trouble lies with the size and shape of the book. The printing is far too small. Further, although a great deal of work has been done in preparing the book, not enough thought has been given to the general arrangement. The lay-out of these two volumes needs to be completely recast.—I am, etc.,

YOUR REVIEWER.

Characteristics of Vision in Fine Work

SIR,—The interesting study (March 18, p. 387) by Ida Mann and Dorothy Archibald of a selected group of women employed on extremely fine work draws attention to certain characteristics of vision which are of special importance for the comfort and success of close workers. These characteristics, and in particular the stereoscopic sense and muscle balance at the near point, are not revealed by the reading of Snellen's types, which is sometimes the only test made in the factory when, indeed, any visual selection test at all is applied. The group studied by the authors came into being, as do many similar groups, "by a process of natural selection," and there is reason for believing that much time is now wasted in giving preliminary training to persons who ultimately prove unsuitable for fine work.

Similar groups of persons employed on fine work were studied by Weston and Adams in a series of investigations made for the Industrial Health Research Board during the period 1927–9, the results being published in three reports.[1 2 3] Their primary aim, however, was to test the value of applying a theoretically probable measure by which the exacting demands made by the work upon the capacity for accommodation and convergence—even when the work is well lighted—would, in effect, be reduced to comfortable limits. This consisted in giving the workers, including those found to be emmetropic and free from phorias, special spectacles with suitable convex lenses and prisms base in.

The groups studied were employed on various fine processes, including linking (hosiery), mounting lamp filaments, and inspecting steel balls for minute flaws. Though most of the workers had long experience and said they were able to do the work without eye-strain, almost without exception, after using the spectacles for some weeks, they reported feeling more comfortable at work and less tiredness of the eyes after the day's work. In nearly every case there was also an increase, often substantial, in their output when the glasses were worn. As might be expected, this increase was generally proportionately greater for persons having errors of refraction or muscle balance, which were also corrected by the glasses supplied, than for persons needing no such correction. Nevertheless, in one process the average increase found was as much as 26% for "normal" persons. The findings in these studies show that the process of natural selection only eliminates the grossly unsuitable individuals. Others, whose characteristics are not so good as they should be—and might be with suitable assistance—carry on with fine work for years, and become so habituated to the strain it occasions that they cease to realize and admit it as such until working without it is experienced.

In their study Mann and Archibald obtained actual dimensions of the task object and the viewing distance in order to establish, on a basis of analysis and measurement, the standard of acuity required for the work. It is encouraging to note this application of scientific method to the problem involved. As yet, a similar procedure has been followed too rarely in dealing with the problems of vision in industry. It was, however, the basis of proposals put forward by Beuttell (1934)[4] for determining necessary values of illumination (and, as Lythgoe showed (1932),[5] visual acuity is a logarithmic function of illumination), and subsequently by Weston[6 7 8] in connexion with standards of both lighting and vision for industry.

Unfortunately, an easily made slip in calculating the size of the retinal image considered by the authors leads them to give a value which is ten times the true size. The error lies in the conversion of the dimension of the gap between turns of the spiral filament from inches to millimetres. The true size of the image of this gap is 0.00025 mm., and the visual angle is 3.125 in. The authors mention the angle 24.14 in. as being usually given for the limit of resolvability. Hence, instead of the retinal image of the gap being larger than the resolvable limit, it is actually well below it. However, "Sherrington has found that osmic-stained nerve fibres of 4 μ diameter are visible to the naked eye,"[9] and, viewed at a distance of 250 mm., an object of this size would give a retinal image of 0.00027 mm. and a visual angle of 3.39 in. It may thus be just possible to see the gap between turns with the naked eye, but certainly the unpractised eye sees a filament of the kind described simply as a single thread and not as a spiral. Using the loupe the authors mention (magnifying about 8 diameters), the image of the gap would be enlarged sufficiently to subtend the limiting angle quoted by them—i.e., about 24 in.

This error, in so far as it affects the authors' conclusion regarding the acuity required for the work, means that a standard better than 6/6—in fact, the best possible—is desirable. There is, however, some doubt whether the detail taken as the criterion of the fineness of the work is really that which the worker normally attempts to discriminate with the unaided eye. Two turns of wire in contact would produce a dark spot in the coiled thread, and, since the diameter of the wire is given as 0.00057 in., such a spot, when viewed at a distance of 250 mm., subtends an angle at the eye of about 25 in. It is probably this, and not the regular gap between two turns of the spiral, which is the "critical" detail. Even so, it remains true that the highest acuity is needed if the work is to be done satisfactorily, and mostly with the unaided eye.

However, it may be inferred from the investigations cited above that even emmetropes with good muscle balance in near vision would derive benefit from the use of convex glasses with suitable prisms for this exacting visual task.—I am, etc.,

London, W.C.1. H. C. WESTON.

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Intelligence and Season of Conception

SIR,—Mr. Penman (April 1, p. 471) points out that Fitt and others have shown that there is an association not only between season of conception and intelligence but also between season of conception and such things as stature, weight, hand-grip, and infant mortality. But he is in error in supposing that this is an objection to the argument of my paper (March 4, p. 320). It is, on the contrary, just what would be expected, because it is well known that these things are positively correlated. What is true of one is likely to apply to all. Mr. Penman might like, however, to have a few figures illustrating these associations from the group of children who provided the data. The correlation between intelligence and stature in a sample of about 800 was of the order of +0.2. In regard to the association between intelligence and early death figures are available for three samples: (1) the brightest 4%; (2) the median 4%; (3) the dullest 8%. The results are as follows:

	Group 1	Group 2	Group 3
Average number of living full sibs * ..	1.95	3.54	5.03
Average number of dead sibs	0.13	0.32	0.53
Average number of stillbirths	0.03	0.10	0.17

* When all mothers have passed the age of 50.

In view of the method of ascertainment the true family size is given approximately by the number of sibs, omitting

in each instance the child who brought the family into the experimental group. Thus the mothers of the dullest children have 2.6 times as many living children as the mothers of the brightest. But they had 4.0 times as many who died before the observations were made and 5.6 times as many stillborn children.

The superiority of winter children demonstrated in the mass studies is to be ascribed to the slight tendency for more intelligent parents to have proportionately more children conceived at that time. Moreover, it is likely to be found that this applies to physique as well as intelligence. It is, of course, possible that this larger effect might mask a smaller one due to a direct seasonal influence on the mother or the developing child. Should this prove true the effect could be in either direction, and, to hazard a guess, it would not be surprising to find (if season of conception does have any direct influence) that for the child of any particular pair it is spring-summer conception which is the more favourable. In this matter it is the less intelligent (and those of poorer physique) who approach more closely to what must be presumed to be the remnants of the natural rhythm. It is difficult, however, to imagine any convincing proof of a direct effect due to season of conception which does not depend on showing that children conceived during a particular season are superior to their brothers and sisters conceived at another.—I am, etc.,

London. J. A. FRASER ROBERTS.

Chronic Pulmonary Catarrh in Childhood

SIR,—In the words of Chevalier Jackson "all is not asthma that wheezes." Taylor (April 1, p. 453) has described a condition in children simulating asthma which he calls "chronic pulmonary catarrh." It is probably the commonest pulmonary condition met with in children who almost invariably give a history of previous lung infection such as pneumonia, measles, or whooping-cough. The condition in the lung is probably comparable to chronic tonsillar infection with cervical adenitis, with which it is often associated, and methods of treatment outlined by Taylor must be tried in an attempt to prevent the attacks occurring while the chest cage is soft and easily deformed. These can best be given at an open-air boarding-school, but unfortunately, owing to lack of accommodation in these schools at the moment, length of stay is usually confined to six months or less. This is quite useless for these "chesty" children, who immediately revert to their attacks on returning home. Although the trouble may not start as a psychological problem, it soon becomes one if the child remains at home in the surroundings of over-anxious parents. I would like to see a sufficient number of open-air boarding-schools established to accommodate these children during their scholastic years, when I believe a high percentage would have few or no further attacks, and be launched on the world with healthy well-formed chests.—I am, etc.,

London, N.W.7. C. ELAINE FIELD.

Marriage and Parenthood

SIR,—Now that the country is becoming alive to the importance of the family unit it is time that the medical profession concerned itself more positively with the prevention of marital disharmony. There are two periods in marriage when much may be done: at the beginning and after the first child is born.

While we pay much lip service to the importance of suitably adjusted partners we do little to encourage their creation, so that far too many marriages go wrong through lack of preliminary teaching. Adequate marriage preparation—which should include the medical examination of both partners, an assessment of their psychological approach to marriage, the state of the hymen, suitable contraceptive advice when desirable, and, above all, education in technique—ought to be taken more seriously by the profession, for there can be little doubt that the seeds of much future unhappiness are often sown in the early months of marriage through ignorance and misunderstanding.

Many conditions such as dyspareunia, impotence, premature ejaculation, and frigidity could be prevented or minimized by a little helpful advice and consideration at this stage. Young people must be encouraged to seek this advice, and the doctor has both a responsibility and an opportunity for much constructive work in this field. More and more couples are asking for help, and yet it is no uncommon thing to find cases which are mishandled and no constructive advice is given. The assurance that all will come right in the end; the suggestion that one or other contraceptive, of which the doctor has read or heard good reports, will be an adequate safeguard; the rapid and often painful examination of the hymen or, occasionally, even the refusal to make such an examination, are neither sufficient nor helpful, and cast an unnecessary slur upon the whole profession. Over and over again one hears people say that their doctors are not interested in these matters.

After the first baby has arrived the couple have various adjustments to make. The problem of effective contraception may present itself for the first time; the resumption of coitus often needs consideration and sympathetic help; the achievement of a mutually satisfactory sex life and the emotional adjustments between mother, father, and child call for careful guidance. While much time is often spent on the problems of mother and child, little is given to those of the husband and wife. Beyond telling the woman that her sex organs have "gone back" to their normal position, that she must take care of herself and not have another child for several months, little constructive help is given. As a result many of the difficulties already enumerated develop or become accentuated. Adequately dealt with all may be well; ignored or glossed over an accumulation of difficulties may create a state of disharmony which will take longer to resolve or even become impossible to correct.

The work of probation officers, matrimonial courts, and such organizations as the Marriage Guidance Council show conclusively that many of these conditions could have been prevented by adequate medical help and effective re-education, thereby not only preventing much physical and psychological injury but saving the marriage and establishing happiness in the home instead of discord.

If the profession would take these matters more seriously and help young couples at these critical periods of their lives many marriages could be saved and the whole stability of family life strengthened. In addition, and as a preliminary to marriage preparation, we must see to it that young people, both in the home and in school and youth organizations, are presented with a positive attitude to sex and marriage through effective education in the psychological, physical, and ethical aspects of sex.—I am, etc.,

London, W.1. EDWARD F. GRIFFITH.

Eye Signs of Anaesthesia

SIR,—I have often seen references to eye-rolling and other movements of the eyes in connexion with inhalation anaesthesia, but have never noticed any eye movements described as nystagmus. I am interested to notice in Dr. E. V. Slaughter's letter (March 25, p. 434) his observations on the development of occasional coarse oscillations.

I have had the opportunity to watch the eyes of children who are being anaesthetized in the upright position with ethyl bromide. In these cases one invariably finds that a true vestibular nystagmus develops just before full anaesthesia is reached. This vestibular nystagmus is almost always in the vertical plane, and the slow phase may be in either direction. Very occasionally it is slightly oblique. The eyes pass into conjugate deviation, usually in the direction of the slow phase, before coming to rest in a central position, as described by your correspondent. Now, all nystagmus of a vestibular pattern must be the result of irritation of the vestibular system; hence the drug employed must irritate either the vestibular centres or tracts, the vestibular nerve, or the labyrinth itself. Skoog of Lund has shown that vestibular nystagmus can be produced by anaphylactic substance, carried direct to the vestibular centres, in the guinea-pig.

Perhaps the anaesthetists could make a careful investigation into these eye movements to see whether vestibular irritation is not apparent with all inhaled anaesthetics. This irritation must take place at a fairly constant level of anaesthesia, and I feel that there is some justification for looking on certain eye movements as an indication of the depth of anaesthesia.—I am, etc.,

Glasgow. TOM O. HOWIE.

Obituary

We regret to announce the death on March 26 at Weston-super-Mare of Dr. GEORGE SAMUEL POLLARD in his 85th year. He was a J.P. for the county of Somerset, had practised in Midsomer Norton and its neighbourhood for 43 years, and was a greatly esteemed member of the Bath and Bristol Branch of the B.M.A., which he joined as long ago as 1885. Dr. Pollard had his professional training at Guy's Hospital, and took the M.R.C.S.Eng. in 1882 and the L.R.C.P.Ed. in 1884, after which he was medical registrar at the Seamen's Hospital, Greenwich. He started practice at Midsomer Norton in 1885, and besides his work as a busy general practitioner he held the post of M.O.H. for the urban area and was for 23 years medical director of the Paulton Hospital. He was also medical officer to Downside Abbey and School. His many activities, professional and other, were commemorated in 1929 when a public presentation was made to him at the time of his retirement; the record is too long to be printed here; few doctors in active practice could have accomplished so much in so many directions. In the British Medical Association Dr. Pollard did good work, mainly in his own county, but many years ago he was for a time a member of the Central Council. He had held office as vice-chairman and chairman of the Bath Division and served on its executive committee. He was a member of the Bath and Bristol Branch Council for 10 years in all and president of the Branch in 1922–3. He celebrated his golden wedding in 1940, and Mrs. Pollard survives him.

Dr. ARTHUR BRIGGS DUNNE, J.P., died on March 27 at Barnby Dun, near Doncaster. He took his B.A. at Cambridge in 1891 and did not begin the study of medicine until some years afterwards. His clinical training was in Leeds and Liverpool. He qualified in 1899, took the Cambridge M.B., Ch.B. in 1902 and the D.P.H. a year later. At Leeds he won the McGill scholarship in surgery and he was called to the Bar by Lincoln's Inn. During the South African War he served as a civil surgeon with the S.A. Field Force, and after his return to England became senior resident medical officer to the City of Liverpool Isolation and Smallpox Hospital. In 1911, after a period as senior school medical officer to the City of Nottingham, he was appointed medical officer of health to the Doncaster Rural Council; in the same year he became M.O.H. for the Bentley Urban District and in 1915 for the Adwick-le-Street Urban District. In 1920 Dr. Dunne was apointed a West Riding magistrate and thereafter attended regularly on the Bench. He retired from his public health posts five years ago.

ALEXANDER ANNAND GREY CLARKE died on March 29 after a short illness at the early age of 34. He was born in India, educated at Marlborough College, and took the B.Sc.Lond. in 1929 when he was aged 19. He then proceeded to Jesus College, Oxford, where he studied forestry, but later became a medical student at St. George's Hospital. After qualification he held the post of casualty officer and house-surgeon at the hospital, took the M.B., B.S. degrees, and was commissioned as surgeon lieutenant, R.N.V.R., early in 1939. On mobilization at the outbreak of war Dr. Clarke was posted to H.M.S. *Courageous*, in which he was serving when his aircraft-carrier was torpedoed and sunk in September, 1939. He was rescued after some two hours in the sea, and subsequently senior naval officers paid tribute to his courage and devotion to duty in dealing with casualties among the survivors. A few months later Dr. Clarke developed meningitis, following recovery from which he was invalided from the Service. He then devoted himself to neurology and psychiatry, and after acting as assistant medical officer at Swansea and Littlemore (Oxford) Mental Hospitals, he took the Diploma of Psychological Medicine in 1941. Early in 1942 he was appointed medical registrar to the West End Hospital for Nervous Diseases, London, where he continued to work until his last illness. He was also an acting assistant physician to the Mildmay Memorial Hospital as well as to psychiatric clinics for children in the Surrey County area. Dr. C. Worster-Drought writes: Alex Grey Clarke was an ideal colleague, a loyal friend, and an enthusiastic worker. His attractive personality, his charm of manner and ready smile will be greatly missed by all his fellow-workers and his patients. He was profoundly devoted to neurology and was especially interested in the more recent therapeutics of early psychoses. Only last year (in conjunction with Dr. F. Prescott) he contributed a paper on the mental and physical manifestations of vitamin B deficiency to the *British Medical Journal*. With his far from robust constitution, the amount of time and energy Alex Clarke put into his work, as well as reading for higher examinations, without doubt lowered his resistance to the infection which cut short a most promising career and one the medical profession could ill afford to lose.

We regret to announce the death of Dr. JAMES DUNLOP WILLIAMSON, M.D., D.L., J.P., a noted figure for many years in the medical and civic life of Belfast. Born at Aghadowey, Co. Derry, Dr. Williamson qualified in 1886 in the old Royal University of Ireland, gaining the degrees of M.D., M.Ch., M.A.O. Two years later he took up general practice in Belfast, later joining the staff of the Ulster Hospital for Children and Women, of which he remained the consulting physician till his death. His long and distinguished period of service to the City of Belfast began in 1900 when he was elected a Councillor. He became High Sheriff and in 1941 deputy Lord Mayor. He served for many years on the Public Health, Tuberculosis, and Maternity and Child Welfare Committees of the Corporation, and his interest in public health led to papers on sanitation and sewage purification. His services to Belfast were recognized when he was made a Freeman of the City a short time before his death. Dr. Williamson had been a member of the British Medical Association for 56 years.

Prof. Grey Turner writes: Dr. FRED B. LUND, who has recently died in Boston, was one of the more senior surgeons of that city, for he was born in 1865 and graduated from Harvard in 1892. For many years he had been associated with the Boston City Hospital and was well known for the work he did in connexion with that institution and his devotion to its welfare. Fred Lund was of a scholarly type and was particularly fond of the study of the history of healing. He made several contributions to the societies and the medical press on historical subjects, and his paper on "Paracelsus," which appeared in the *Annals of Surgery* for October, 1941, will remain as an evidence of his learning and interest. Just recently he informed me that once again he was reading the works of the Venerable Bede, and I looked forward to the opportunity of acting as his guide on a long-contemplated visit to the home of that great pillar of early English learning at Jarrow-on-Tyne. He loved this country and was very happy indeed in making acquaintance with those parts of England and Scotland with which he had become familiar through our literature, and was longing to be spared to make just one further visit. Lund accompanied the Society of Clinical Surgery of America to this country in 1910 and acted as its reporter, and from then onwards he kept in friendly touch with many of the leading surgeons of Great Britain. In his home city he took a great interest in the medical societies and had been president of both the Massachusetts Medical and the Boston Surgical Societies. To the *Transactions* of these bodies he often contributed, and as a rule on some historical subject. Lund was an original Fellow of the American College of Surgeons and a member of several of the societies; he also took a great interest in the *New England Journal of Medicine*. He was a great host and loved to entertain his friends, and liked nothing better than to show visitors from this side the venerable parts of Boston, of course never forgetting the ether theatre in the Massachusetts General.

Medical Notes in Parliament

EDUCATION BILL

Medical Inspection and Treatment

In Committee on the Education Bill on March 23 the House of Commons examined Clause 46 (Medical Inspection and Treatment of Pupils). Mr. LINSTEAD moved to add "dental and optical" where the clause referred to "medical." The country as a whole would long suffer from a shortage of dentists. There were only 650 medically qualified ophthalmic practitioners for over 5,000,000 school children. Many defects of vision were missed. That raised the question whether the services of sight-testing opticians should be used to supplement the services of the ophthalmologists. Dr. HADEN GUEST supported Mr. Linstead provided that if people not medically qualified were to make examinations this should be regarded as a provisional arrangement.

Mr. BUTLER said the school medical services would be better if there were more doctors, but they had to suffer from the needs of the Armed Forces. In many areas it was the practice for an optician to attend with the ophthalmic surgeon when children's eyes were examined. Opticians were not doctors, and he must insist that the general examination of children for eye troubles should be done by ophthalmologists and not by somebody solely concerned with the making up of prescriptions. Captain PRESTCOTT said he was informed that inspection of eyes in the school was often now done by a nurse or even by a

teacher. There were 7,000 opticians and they would be of great value if employed, at least in part, for this purpose. Mr. BUTLER reaffirmed that the Ministry could not substitute opticians for ophthalmologists in important cases. They were used and would continue to be used.

Mr. Linstead withdrew his amendment.

Sir E. GRAHAM-LITTLE moved and withdrew an amendment which proposed that the Act should not be construed as imposing an obligation on any parent to submit his child to medical examination or treatment. On this Mr. Butler remarked that compulsory inspection was a novelty, but one to which he attached particular importance. He proposed and the House accepted an amendment to provide that if the parent of any pupil gave to the authority notice that he objected to the child's availing himself of any medical treatment the pupil should not be encouraged or assisted so to do.

On the motion that Clause 46 stand part of the Bill, Dr. HADEN GUEST suggested that Mr. Butler should insert later a provision that a medical inspection should be made not fewer than three times in the school career. He also asked Mr. Butler to consider the possibility of a new clause to give the school medical officer the opportunity to inspect the child's home conditions if he thought its state arose from something within the home. It was important to see that there was adequate sleeping accommodation for the child. In the course of his duties he had often unofficially entered homes and had never been refused by parents. Mr. BUTLER said the Government preferred to leave the Bill as drawn. A large majority of the children were covered in some way in the routine of inspections in a normal year before the war. The Government did not think it right to impose an extra duty on the school medical officer to go into people's homes. Under Clause 73 a school doctor could go into the home of a child having a disease so serious that it was impossible to educate the child at school.

Sir E. GRAHAM-LITTLE asked what would be the position of the family practitioner if the arrangements in this clause were carried out. If the inspection and treatment of children from 2 to 18 was to be the function of the school medical officer, without any reference to the family practitioner, an unfortunate position would arise. So great a step in the medical treatment of children should not be taken until Parliament had further knowledge of what would happen to the general health service.

The House then agreed to the clause.

Position in Non-Maintained Schools

During the continued discussion on March 28 Mr. EDE moved an amendment to Clause 73 to make arrangements by which the proprietor of any non-maintained school could secure the benefits of medical inspection and treatment. Dr. HADEN GUEST said there was no doubt that some small private schools badly needed the medical inspection and treatment, and also some public schools. He asked what steps the Board of Education proposed to take to see that there was such inspection in these schools.

Mr. EDE pointed out that the Bill gave the Board the power, for the first time, to inspect the kind of schools Dr. Haden Guest had mentioned. If they found that a school was being used, as it sometimes was, in order to object to such things as medical inspection and treatment—he was now talking of the worst types of private schools—that might be one of the items on which a report could be made by the Board. They would expect the proprietor of the school, within the limit of six months allowed, to make such arrangements as were necessary to secure the benefits of medical inspection for the pupils attending his school. Similarly, if meals were not provided where they should be, the same kind of machinery would be brought into operation. Dr. HADEN GUEST asked if it would be possible for a school to refuse to have medical inspection, and Mr. Ede replied that if it did, that might very well be a ground, under the Private Schools Clause, for bringing it before the tribunal, with a view to having the school closed. The amendment was agreed to.

Vaccination

On Clause 74 (which makes supplementary provisions with regard to medical inspection and treatment) Mr. VIANT moved an amendment to ensure that nothing in the Bill should be used for ascertaining the vaccinal condition of the children or their condition in respect of any other form of inoculation, for securing the performance of such inoculations, or for the imposition of mass radiography or any other medical procedure. He said there was considerable apprehension among many parents about the powers which were being conferred on the Board of Education in regard to medical inspection and treatment. There was nothing like unanimity of opinion, even in the medical profession, about vaccination and inoculation. Dr. HADEN GUEST expressed the hope that the Minister would not accept the amendment, which was so widely drawn that it would create considerable difficulties. Mr. MESSER expressed the hope that the Board would consider the advisability of ensuring that medical examination should include mass radiology.

Mr. EDE said that the amendment was not necessary. Nothing would be done under the clause or in the Bill to compel a child to be vaccinated or inoculated, or to undergo any of the other procedures mentioned in the amendment, without the consent of the parent. The amendment was withdrawn.

Malnutrition in Occupied Countries

The ARCHBISHOP OF CANTERBURY, in the House of Lords on March 15, asked for information about the supply of food to enemy-occupied countries. He said that what had been done in Greece had probably saved the lives of 2,000,000 people. He proposed that in Belgium the Allies should supply the medical requirements to prevent serious deterioration of health. He understood that vitamins were treated as medical supplies, and that it was possible to pass them through, whereas dried milk was treated as food. In Poland it seemed that children up to the age of 3 were tolerably well fed, in order that they might be German citizens in future. In Greece 1,800,000 children needed swift help; in Holland about 300,000; in Poland 3,500,000; in Czechoslovakia 1,600,000; in Yugoslavia 2,100,000. These were figures for young children.

Lord HORDER said clinical examination of refugees reaching this country or Lisbon showed conditions only produced by prolonged malnutrition, including hunger oedemas. The calorie value of a day's food required for health was 2,480. In September, 1943, the basic daily ration in Belgium was about 1,260 calories—about half the ration in that country during the war of 1914–18. In France the calorie value at the end of 1943 was about 1,080. Children in Belgium under 6 years received supplements. These were withdrawn at 6. Adolescents from 14 to 21 were suffering most. Adults, according to a large investigation of the Liége Polytechnic, had lost 20 to 34 lb. weight, and protein substances in the blood showed a fall of from 20 to 50%. Pregnant women showed a drop of 80% in the normal weight gain, and infants at birth an average dron in weight of 2.2 lb. Students, nurses, and hospital personnel showed malnutrition. In Belgium, between December, 1941, and February, 1943, the rise in the incidence of tuberculosis was 58.5%. Fulminating pulmonary tuberculosis was to-day experienced in Belgium, France, and Greece. He understood the Nazis had not prevented the food supplies sent to Greece from reaching the people for whom they were intended. Why not try elsewhere?

The EARL OF SELBORNE, replying for the Government, said that the Government had endeavoured to mitigate the effect of the blockade to its allies. It had taken vitamin D off the contraband list. Occupied Europe was one economic unit and was worked by the Germans as such. Therefore he knew no reason why relief should be confined to Belgium. In that country in 1914 the death rate per 1,000 was 14.14. By 1918 it was 20.82. In 1939 it was 14.14; in 1942 it was 14.3. For the first half of 1943 deaths were at the rate of 13.0 per 1,000, although the Germans had deported the strongest and healthiest section of the community. In 1929 the infant mortality rate in Belgium was 104 per 1,000; in 1939, 73 per 1,000; and in 1942, 78. It was impossible for anybody in Europe, or in any other country, to control the distribution of food to necessitous cases. Could a reasonable man doubt that the Germans would avail themselves of the amount of food going into a country in order to manipulate the basic ration so that the benefit of the imported food rebounded to them? Allied experience in Greece had not been such as to encourage the British Government to think that control of that kind would be easy to administer in other parts of occupied Europe. But if circumstances allowed the British Government to mitigate the lot of its allies without injuring its war effort, it would gladly take advantage of the opportunity.

Maternity Accommodation

Mr. WILLINK stated, in the course of a reply on March 30, that in 1938 there had been in England and Wales 11,500 maternity beds. To-day there were 15,500 and also 2,500 emergency maternity beds. In addition, 500 other beds had been approved. The beds available before the war took approximately one-third of the births. Those at present available took one-half of them. That was equal roughly to the all-over increase in demand.

Serving Doctors' Practice Losses

On April 4 Sir E. GRAHAM-LITTLE asked the Secretary of State for War if he was aware that many doctors on joining the Forces in 1939 lost their practices which, in many cases, they had purchased with the aid of loans, charges on which they had to meet out of Service pay; and if he would give an assurance that in such cases compensation would be paid after the war equal to the pre-war value of their practices. Sir

JOHN ANDERSON, who replied, said: Losses of this nature affecting many different sections of the community are among the distressing consequences of a war such as that in which we are now engaged, and I clearly could not single out one particular class of case for exceptional treatment in the manner proposed.

Increase in Illness among Women Civil Servants

On April 4 Mr. BARTLETT asked the Secretary to the Treasury to what extent information in his possession corresponded with the common experience of medical practitioners that there had recently been an increase of illness among women civil servants due to fatigue; and whether he would be prepared to authorize heads of Departments to exercise discretion in suitable cases for the reduction of hours in modification of instructions given at a time when the national crisis was in its most acute stage. Mr. ASSHETON: Owing to shortage of staff complete annual sick rate returns for the Civil Service are not available. Such information as I have shows definite increase in sick absence over pre-war rates, and on the whole greater increase for women than for men, but the increase varies in different sections and localities, and is not, over all, very great. Heads of Departments have discretion in regard to hours, but, in view of the acute and increasing man-power shortage, they are not able to reduce hours generally.

Notes in Brief

Mr. Peat stated on March 2 that during recent weeks there had been a substantial increase in the supply of sulphathiazole available for civilian use. Production should now be adequate to enable all prescriptions to be met. It was now available, on a prescription, to everybody.

Mr. Willink proposes to issue a summary report of the Ministry of Health for the year ending March 31, 1944, but is unable at present to indicate the date.

The number of doctors in the *Medical Register* at the end of last year was 71,882. This figure includes many who are not normally resident in the United Kingdom or who have retired from practice, as well as those registered, temporarily or otherwise, by virtue of Empire or foreign qualifications.

In the House of Lords on March 1 the Income Tax (Offices and Employments) Bill and the Disabled Persons (Employment) Bill received the Royal Assent.

EPIDEMIOLOGICAL NOTES

Discussion of Table

In *England and Wales* notifications of measles and whooping-cough showed the greatest fluctuations, with totals higher than last week's by 531 and 218 respectively.

The rise in whooping-cough was general throughout the country, but was especially marked in Essex and Flint, where the total notifications exceeded those of last week by 31 and 24. The increase in measles was most noticeable in the south, especially in Kent, Isle of Wight, London, and Sussex, whose total notifications exceeded those of last week by 111, 84, 77, and 35 respectively. Durham also recorded a big rise—47—over last week's total. In Lancashire the notifications of measles dropped by 64. The total notifications of cerebrospinal fever were 14 more than last week, and the incidence of this disease is at its highest level for the past year.

There were 5 more cases of dysentery: during the past seven weeks the notifications have averaged 243 per week. The largest returns were those of Lancashire 62, London 32, Derbyshire 32, Surrey 26, Middlesex 16, Essex 11, Yorks West Riding 10.

Two cases of smallpox have been reported in Pudsey, Yorkshire.

In *Scotland* there were rises of 19, 32, and 34 in the total incidence of dysentery, measles, and scarlet fever, but a fall in incidence was reported for whooping-cough 26, and diphtheria 13. The 136 cases of dysentery were only 5 below the very high total of six weeks ago. The largest returns were: Lanark County 36, Glasgow 36, Edinburgh 15, Dumfries County 15, Dundee 12. The only large local variations in the incidence of measles were increases in the towns of Greenock of 35, and Paisley of 26, and a decrease in Glasgow of 33.

In *Eire* rises in the notifications of diphtheria by 24, and of measles by 78, were recorded. The rise was general throughout the country except in Dublin C.B., where measles declined by 37 cases.

Week Ending April 1

The returns of infectious diseases in England and Wales during the week included: scarlet fever 2,450, whooping-cough 2,141, diphtheria 724, measles 2,643, acute pneumonia 1,277, cerebrospinal fever 86, dysentery 309, paratyphoid 0, typhoid 5, smallpox 1. Deaths from influenza numbered 32.

No. 12

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended March 25.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1944					1943 (Corresponding Week)				
	(a)	(b)	(c)	(d)	(e)	(a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	101	13	16	6	4	101	8	31	3	5
Deaths		1	1				2	2		
Diphtheria	666	32	174	107	41	816	37	207	91	25
Deaths	10	—	5	4	1	21	2	1	1	—
Dysentery	274	32	136	—	1	92	10	37	—	1
Deaths				—	—				—	—
Encephalitis lethargica, acute	—	—	1	—	—	1	—	—	—	—
Deaths		1					1			
Erysipelas			43	21	3			50	15	13
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				4					18	
Deaths	52	5	12	13	3	56	5	3	15	7
Measles	2,757	363	377	374	5	19,561	1,329	718	27	117
Deaths	—	—	1	6	—	18	6	5	—	—
Ophthalmia neonatorum	82	3	21	1	2	96	5	27	—	—
Deaths										
Paratyphoid fever	6	—	—	—	—	1	—	3	—	1
Deaths	1	—	—	—	—	—	—	1	—	—
Pneumonia, influenzal*	1,270	86	11	7	8	1,505	80	12	16	—
Deaths (from influenza)	44	2	4	2	1	73	7	2	1	—
Pneumonia, primary			270	38				281	33	9
Deaths		70		18	26		—		19	15
Polio-encephalitis, acute	2	—				1	—			
Deaths		—					—			
Poliomyelitis, acute	7	—	—	—	—	4	—	—	1	—
Deaths		—					—			
Puerperal fever		3	21		—		1	5		—
Deaths										
Puerperal pyrexia†	170	10	22	4	2	191	7	10	2	1
Deaths		—					1			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	2,389	169	281	29	82	2,185	156	262	53	39
Deaths	1	—	—	—	—	4	—	—	—	—
Smallpox	1	1	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever	9	—	—	11	3	6	—	5	5	2
Deaths	—	—	—	—	—	—	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	7	—
Deaths				—	—				—	—
Whooping-cough	2,244	222	104	94	11	1,982	186	224	75	32
Deaths	10	4	—	6	—	19	1	1	2	2
Deaths (0–1 year)	451	63	84	58	28	469	55	62	40	42
Infant mortality rate (per 1,000 live births)										
Deaths (excluding still-births)	5,500	1,028	631	325	160	5,269	889	606	252	143
Annual death rate (per 1,000 persons living)			14·5	21·2	‡			13·7	16·6	‡
Live births	7,467	859	959	446	274	6,410	786	897	410	349
Annual rate per 1,000 persons living			19·5	29·1	‡			18·3	27·0	‡
Stillbirths	257	28	31			252	19	37		
Rate per 1,000 total births (including stillborn)			31					40		

* Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

† Includes puerperal fever for England and Wales and Eire.

‡ Owing to evacuation schemes and other movements of population, birth and death rates for Northern Ireland are no longer available.

The Services

A meeting of the subscribers of the Naval Medical Compassionate Fund will be held on Friday, April 28, at 3 p.m., at the Medical Department of the Navy, 64, St. James's Street, London, S.W., to elect six Directors of the Fund.

The *London Gazette* has announced the appointment as M.B.E. (Military Division) of Capt. S. D. Stock, R.A.M.C., in recognition of gallant conduct in carrying out hazardous work in a very brave manner.

CASUALTIES IN THE MEDICAL SERVICES

Wounded.—Temp. Lieut.-Col. G. S. N. Hughes, I.M.S.; War Subs. Capts. J. W. R. Battram, R. A. S. Gibb, B. C. M. Palmer, R.A.M.C.

Prisoners of war.—Temp. Major P. V. MacGarry, R.A.M.C.; Acting Major E. L. Ellis, R.A.M.C.; War Subs. Capts. J. E. A. Bartlet, D. Benson, C. F. Campbell, G. M. Davies, T. E. Marshall, C. R. Robson, and R. D. Taylor, R.A.M.C.; Lieut. J. Markowitz, R.A.M.C.

Died on active service.—Lieut.-Col. F. A. Roddy, R.A.M.C.

Universities and Colleges

UNIVERSITY OF EDINBURGH

Chair of Public Health

As briefly announced in the *Journal* of April 1 the University Court has appointed to the Bruce and John Usher Chair of Public Health Prof. F. A. E. Crew, M.D., D.Sc., F.R.C.P.Ed., F.R.S., in succession to Prof. P. S. Lelean. Since 1928 Prof. Crew has occupied the Chair of Animal Genetics; in recent years he has devoted attention to the problems of social biology and social medicine, and his appointment to the Bruce and John Usher Chair marks an important new development in medical teaching and research in Edinburgh.

For many years after the Public Health Services became an established feature of national administration, the orientation of these services was mainly towards prevention of the specific infectious diseases, and the teaching of public health in the medical schools became centred on environmental hygiene and the control of infection. While the medical undergraduate must be taught the elements of these subjects, instruction in the technicalities of public health practice is a subject for postgraduate study, and in recent years the need for a different approach to the study of health in the undergraduate curriculum has been appreciated. The developments in the health services forecast in the Government White Paper indicate that medicine must play an ever-increasing part in the future social life of the people, and a new outlook has emerged under the designation Social Medicine. It is not enough to protect the public individually and collectively against the epidemic diseases, but health of body and mind must be created and preserved by all possible means. Many adverse factors in modern society, particularly among the industrial population, are playing a tremendous part both directly and indirectly in causing ill-health and unfitness. Advances in knowledge of nutrition in relation to social conditions have revealed certain of these factors. The facts recently brought to light on infant mortality in Scotland are a tragic reminder of the existence of such adverse conditions in the social life of the people.

In the future medical curriculum in Edinburgh it is proposed to develop the teaching of these aspects of medicine—namely, social biology, social medicine, and positive health. The task of developing such teaching has been entrusted to Prof. Crew, who will bring to his future academic work a wide knowledge of biological science, on the principles of which all health studies must be based, and a deep interest in the problems of social biology and medicine. Along with this new teaching on health the undergraduate will receive instruction as before in the elements of environmental hygiene, public sanitation, and the control of communicable diseases. By arrangement between the University and the Corporation of Edinburgh, the Medical Officer of Health, Dr. W. G. Clark, and the staff of the Public Health Department of the City will undertake the main part of this teaching in co-operation with the new professor; and in the postgraduate curriculum for the D.P.H., Dr. Clark and his staff will be responsible for all the technical instruction in public health practice and administration. The teaching to be undertaken by Prof. Crew and that of Dr. Clark will be complementary, and both courses together will form the basis of future teaching in Edinburgh in the wide field of health and social medicine. In creating and developing this University School of Health other academic departments will contribute, such as those of Child Life and Health, Tuberculosis, Psychiatry, Social Study.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS

At a meeting of the Royal Faculty of Physicians and Surgeons of Glasgow held on April 3, the President, Dr. James H. MacDonald, in the chair, the following were admitted Fellows of Faculty *qua* Physician: W. S. Bell, M.B., T. G. Brown, M.B., D.P.H., P. R. Peacock, M.B., W. N. Rogers, M.D., W. T. Strauss, M.D.

The following were admitted Fellows of Faculty *qua* Surgeon: G. B. Mair, F.R.C.S.Ed., G. H. Stevenson, F.R.C.S.Ed.

Medical News

The London Jewish Hospital Medical Society and the Jewish Emergency Medical and Dental Association will show a film entitled "Red Army Medical Service" in the Hastings Hall at B.M.A. House, Tavistock Square, W.C., on Sunday, April 16, at 3 p.m. Speakers: Prof. S. Sarkisov (Russia), Prof. Samson Wright, and Mr. Ingram Lindner.

A meeting of the London Association of the Medical Women's Federation will be held at 26, Portland Place, W.1, on Tuesday, April 18, at 7.45 p.m., when Dr. Neville Goodman will speak on "Problems of Health in Europe." Medical guests are invited. A meeting on the White Paper is being arranged for May.

The British Institute of Radiology will hold a meeting of medical members in the Reid-Knox Hall, 32, Welbeck Street, London, W., on Friday, April 21, at 2.30 p.m. On April 22 at the same hour Dr. J. Blair Hartley will read a paper on "The Future of Radiology in Obstetrics."

A Diagnosis Section meeting of the Faculty of Radiologists will be held at the Royal College of Surgeons of England, Lincoln's Inn Fields, W.C., on Saturday, April 22, at 10.30 a.m., when papers will be given by Major D. C. Eaglesham, R.C.A.M.C., on "Observations on Opaque Myelography of Lumbo-sacral Disk Herniations," and Dr. A. M. Rackow on "Some Problems of Appendix Radiology," to be followed by a discussion.

The Food Education Society will meet on Monday, April 24, at 3 p.m. at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C., to hear a public lecture on "Food and the Teeth" by Sir Norman Bennett.

The spring meeting of the British Orthopaedic Association will be held in Leeds on Friday and Saturday, May 12 and 13. The morning session (9.15 a.m.) on Friday—to be held in the Physiology Lecture Theatre at the Medical School—will be devoted to papers read by Leeds men. In the afternoon (2 p.m.) there will be a clinical demonstration at the Infirmary by members of the staff. On Saturday (9.15 a.m.)—again in the Physiology Lecture Theatre—a business meeting will be followed by the reading of short papers by medical officers in the American and British Armies.

There has been formed a Polish Medical Association in the United Kingdom with its seat in London. At a general meeting held on March 26 in the Great Hall of B.M.A. House, to which about 400 Polish doctors now in this country were invited, the following were elected: Hon. President, Dr. George de Swiet; Chairman of Council, Dr. C. Meissner; Secretary, Dr B. Jedlewski. The address of this organization is B.M.A. House, Tavistock Square, W.C.1.

The Council of Management of Preston Hall, British Legion Village, Maidstone, Kent, has appointed Dr. J. Douglas Robertson, D.Sc., Ph.D., M.R.C.P., F.R.S.Ed., as clinical pathologist to the British Legion sanatoria, and Mr. A. T. Fripp, F.R.C.S., as visiting orthopaedic surgeon in connexion with the new wing at Nayland Sanatorium, which will accept female patients with non-pulmonary conditions for treatment.

Major Sir Brunel Cohen has given £1,000 towards the cost of an *x*-ray unit at Nayland Sanatorium which was taken over by the British Legion on May 1, 1943. It is proposed to establish this unit in the new treatment centre which will be built as soon as permission is obtained for its erection. Sir Brunel Cohen has for long been identified with the work of the British Legion in this country, is Treasurer of the British Legion, a former Member of Parliament, and himself a severely disabled ex-Service officer from the last war.

Lord Nuffield and the Trustees of the Nuffield Foundation have authorized grants amounting to approximately £9,000 to the Potato Research Scheme. The production of varieties resistant to disease is work of the highest importance to this country, and other countries in the Empire need varieties suited to their conditions. Scientific work has shown that these diverse qualities desired must be sought among potatoes indigenous to Central and South America. A very large collection of such types, wild and cultivated, has been formed at the School of Agriculture, Cambridge, and scientific investigation of them started.

Letters, Notes, and Answers

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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ANY QUESTIONS?

More about the Rh Factor

Q.—*I have a patient aged 30 whose first child was normal in all respects. Her second baby died of haemolytic disease of the newborn. She was advised by her doctor at that time not to have any more children. She is keen to have another child, and I feel that there is an even chance of its being born normal, and should it show any signs of haemolytic disease it stands a very good chance of survival as a result of recent advances in our knowledge. What advice should I give?*

A.—If the father is heterozygous (Rhrh) there should be an equal chance that any subsequent pregnancy will produce an Rh-negative normal baby, although the birth of a normal child immediately after one suffering from haemolytic disease is said to be uncommon. If the father is homozygous (RhRh) every child born subsequently will be affected; the first child was normal because the mother had not then developed sufficient anti-Rh agglutinins to produce haemolysis. Help in determining the genotype of the father may be obtained by testing their child, since, if it is Rh-negative, the father must be heterozygous. If, however, the child is Rh-positive, further help can be obtained by determining the father's Rh subgroup; thus St serum agglutinates the red cells of 80% of people, including all negative people and all those (48%) who are heterozygous; therefore the remaining 20% of people whose red cells are not agglutinated must be homozygous (see article by G. L. Taylor and R. R. Race in the *Journal* of Feb. 26, p. 228). Actually, since 38% of people are homozygous this test will discover over half of them, but it can be carried out in only a few laboratories.

Should the parents have another child and it develops haemolytic disease of the newborn, the immediate prognosis would be a good one if the child were given prompt and adequate transfusions with Rh-negative blood, but we do not yet know whether such treatment will prevent the occurrence of kernicterus or cirrhosis of the liver. In previous years, when regard was paid only to ABO grouping, kernicterus occurred in about 8% of cases; but evidence should be forthcoming in 2 or 3 years' time to show whether this incidence is diminished by the use of Rh-negative blood. The possibility that the child may develop kernicterus or cirrhosis must be clearly understood by the parents should they decide to have another child, but the risk that haemolytic disease may manifest itself as hydrops foetalis is so small that it can be disregarded.

Oiling Blankets

Q.—*May I have details of the technique of oiling blankets to prevent the disturbance of fluff, dust, etc., or alternatively a reference where this is given? What I have in view is avoiding such contamination of the air in the operating theatre.*

A.—Recent work has shown that blankets may be grossly contaminated by droplets expelled by streptococcal and staphylococcal throat and nose carriers, and that, during bed-making or when the bed is merely being tidied, the dried bacteria-containing droplets are raised into the air and may produce infection by inhalation or by falling on susceptible tissues such as open wounds or burns. A contaminated blanket brought into the operating theatre with a patient may therefore be a means of infecting intentional wounds. The fluff of blankets is also the chief contributor to the dust of hospital wards. Van den Ende and his colleagues (*Lancet*, 1941, **1**, 716) had found that spindle oil, a crude liquid paraffin, could when rubbed into wooden or lino-covered floors prevent bacteria-infected dust being raised into the air during sweeping. This principle was applied to textiles, at first using purified liquid paraffin in white spirit, and later "technical white oil" with an emulsifying agent which allowed an oil-in-water mixture. Recipes for the preparation of these oil emulsions may be found in the report by van den Ende and Thomas (*Lancet*, 1941, **2**, 755); a ready-made oil emulsion, olinol No. 1, is available from the Manchester Oil Refinery Ltd.

In practice 20% of the oil emulsion is added to the last cold-water rinse in the washing machine. The blankets are treated for 20 minutes, when they are transferred to the hydro-extractor, from which the oil-in-water effluent may be salvaged for further use. Though they now contain 3 to 5% of oil, the treated blankets can scarcely be differentiated from unoiled blankets. Besides the physical adsorption of dust particles, the oiled blankets may, depending on the emulsifying agent, be bactericidal as well to bacteria in moist droplets. In any case the oiling of blankets and other textiles will reduce by 99% the number of bacteria liberated during vigorous shaking. Blankets in constant use need to be re-oiled once a month, but not necessarily after sterilization, which, incidentally, should be done at a pressure not exceeding 5 lb. in order to avoid damage to the wool. Further technical improvements will doubtless increase the practicability of using oiled bed-linen for preventing dust-borne infection.

Fore and Aft

Q.—*What are the modern views on the relation (if any exists) between the pelvic viscera or the abdominal contents and the pharynx and its accessory structures? Some thirty years ago, when I was a student, we used to be told about a "prostatic cough," due, I understood, to some kind of influence of an enlarged prostate on the cough mechanism. I have also seen references to a similar cough produced by some uterine conditions, and to "fullness in the head," rushing and roaring noises in the ears, and other slight but not necessarily insignificant symptoms produced by distension of the colon and other forms of constipation. Is all this imaginary or subjective, or has any anatomical connexion, conceivably by way of the circulatory system or the autonomic nervous system, been demonstrated between the pelvic viscera or the abdominal contents and (a) the cough mechanism or (b) the ear and its accessory structures? Or perhaps one might put it: Has any anatomical connexion been demonstrated between the upper and lower ends of the alimentary canal and their accessory structures?*

A.—No special connexion of the kind is known. Cough is not a common symptom of prostatic disease, and it would suggest that the lesion had led to uraemia. Widespread effects may be produced by distension of the rectum—salivation, nausea and vomiting, mental depression, restlessness, mental haziness, and inability to concentrate. The power of ocular accommodation may be reduced, and measurable changes such as distension of veins and oedema have been described in the retina. These effects show that the rectum is an unusually sensitive organ, and that when it is stimulated a strong stream of impulses flows into the central nervous system and radiates over a considerable area. Sudden death has occurred from distension of the uterus with bland fluid in the attempt to produce abortion. All this indicates that reflex disturbances occur when the pelvic viscera are stimulated, but it does not indicate any special anatomical connexions. An endocrine relationship appears to exist between the nasal mucosa and the sexual organs. Female monkeys show a cyclical activity of the nasal mucosa which is synchronous with the periodic swelling of the sexual skin, and oestrogens have been used in the treatment of atrophic rhinitis. This relationship has some bearing on the phenomenon of vicarious menstruation.

Pregnancy and Tuberculous Spine

Q.—*Is it advisable for a woman aged 32 years, who had tuberculosis of the spine, to marry? And if so, is it advisable for her to have a child? The person concerned was regarded as "cured" about twelve years ago. What is the probability of a recurrence under normal living conditions? Is either of the above factors likely to have any effect in increasing probability?*

A.—There is undoubtedly a tendency for bone tuberculosis to become active during pregnancy. I know of a case of tuberculosis of the dorsal vertebrae, treated by bone graft some years previously, in which a fatal miliary tuberculosis developed at the end of pregnancy; and I have hearsay knowledge of three other somewhat similar cases. On the other hand, there are many examples of women with old-standing Pott's disease of the spine who have passed uneventfully through pregnancy and the puerperium. Much depends upon the time that has elapsed since there has been clinical or radiological evidence of active disease. To forbid pregnancy in every circumstance will cause needless unhappiness and may lead the patient to feel that her mission in life has remained unfulfilled. On the other hand, to ignore the danger is equally reprehensible. In this case, if twelve years have elapsed since there was evidence of activity (this should include radiological examination), it seems reasonable to allow a pregnancy, other things being equal. The patient must be made to realize the paramount importance of regular adequate rest and of good diet during her pregnancy; milk intake should be specially liberal in order to prevent a possible fall in blood calcium.

The above remarks must be taken only as a general guide. Without full knowledge of the patient, her general condition, her personal circumstances, and so forth, it is not possible to give either a plain "Yes!" or an emphatic "No!"

Puerperal Fever and Streptococci

Q.—*It has usually been supposed that a case of scarlet fever in a household constitutes a danger to a woman who is about to be or has been confined in that household, because of the danger of puerperal fever. Is there any evidence that the causative haemolytic streptococcus in puerperal fever is in fact one of the types causing scarlet fever? It has been suggested that the response to sulphanilamide treatment in puerperal fever and the lack of response to such treatment in scarlet fever indicates a difference in the causative organism.*

A.—There is no doubt that any haemolytic streptococcus causing scarlet fever or streptococcal tonsillitis is capable, given the opportunity, of producing infection in the genital tract of a parturient woman. The common scarlatinal strains—Griffith's Types 1, 2, 3, and 4—have all been isolated from cases of puerperal infection, and, of course, some of the affected patients develop scarlatinal rashes. Therefore, when a woman acquires a streptococcal puerperal infection, inquiry should be made about any sore throats in the household, and all family contacts as well as the attendant midwife or doctor should have nose and throat swabs examined for haemolytic streptococci.

The failure of scarlet fever to respond to sulphonamide therapy is due to the fact that it is essentially a toxaemia accompanying a local throat infection, whereas puerperal sepsis is an invasive infection of the uterus by the haemolytic streptococcus, and this type of streptococcal infection (compare, for example, erysipelas) is particularly amenable to treatment with sulphanilamide.

Vaccination and Encephalitis

Q.—*Is there any danger in revaccinating young adults? Was there not a scare some years ago when several cases of encephalitis followed revaccination? Is this danger great? How can it be avoided?*

A.—Encephalitis is a very rare complication of vaccinia. The Committee on Vaccination (1928) reported an incidence in England of 1 : 48,000, and in Glasgow during 1942, when about half a million persons were vaccinated, the incidence was approximately 1 : 70,000. It occurs almost entirely after *primary* vaccination, although 1 of the 7 Glasgow cases recorded by Anderson and MacKenzie (*Lancet*, 1942, **2**, 667) was a woman aged 41 who had been successfully vaccinated in infancy. Children over 5 and young adults are the age groups principally affected. There is no evidence that the encephalitis is associated with any special batch or preparation of lymph. Its greater frequency in England and Holland from 1923 to 1928 suggests that there may be a certain epidemicity in its occurrence. No conclusion has been reached as to whether the encephalitis is caused by the original virus—it follows other virus infections, particularly measles and mumps—or is due to the activation of a latent virus. Symptoms, varying from severe headache and drowsiness to deep coma, usually develop within 7 to 14 days after vaccination, and recovery, when it occurs, seems to be complete without sequels. Convalescent serum or antivaccinal horse serum may be used for the treatment of severe infections. Avoidance of the complication can best be effected by avoiding primary vaccination in school-children and adolescents. If this is impossible, a single linear insertion instead of multiple insertions should be carried out in such cases.

Atrophic Rhinitis

Q.—*A man of about 40 has had atrophic rhinitis for the past 20 years. I would be grateful for suggestions regarding treatment.*

A.—The most satisfactory local application is glycerin containing 25% of glucose. Benians showed that the organism associated with atrophic rhinitis does not grow in carbohydrate, which encourages the growth of the harmless *Staphylococcus albus*. This answers well when applied in practice, but crusts should be removed.

Trichomonas vaginalis

Q.—*Is infection by Trichomonas vaginalis becoming more common? How is it usually acquired? Is it limited to the vagina in females? Are male subjects liable to infection? How is it recognized? What is the best treatment?*

A.—There is no doubt that infestation by *Trichomonas vaginalis* is either becoming much more common or is being diagnosed more frequently. It seems probable that gynaecologists and venereologists are on the lookout for it much more nowadays than formerly. It is not known how it is acquired, but some regard it as venereal in origin. Apparently it is often present in the normal vagina, but gives rise to symptoms mainly when the *p*H is about 6 (normal 4–5). It is usually limited to the vagina in females, but may affect other parts of the urogenital tract, especially the urethra. Males are liable to infestation, but the condition is either not common or rarely gives rise to symptoms.

Lister and Lees found *Trichomonas vaginalis* in 4% of 400 consecutive cases (excluding syphilis) attending a V.D. out-patient department and in 16% of 105 cases of diseases of the genito-urinary system (excluding gonorrhoea). The diagnosis depends on demonstration of the organism. This is done by means of microscopical examination of: (*a*) moist films, preferably with the dark-ground microscope; (*b*) cultures; (*c*) films stained by Leishman's method. The first is probably the most satisfactory method for anyone but an expert.

Treatment consists in producing conditions unsuitable for the growth of the organism. In the male alkalinization of the urine by means of sodium bicarbonate by mouth often suffices, but in females various other methods are usually required. These include silver picrate in the form of powder for insufflation and pessaries; tablets of pentavalent arsenic for insertion in the vagina, combined with alkaline douches, or "negatol" in the strength of 2½% for douches and 100% for painting.

Eczema in a Child

Q.—*What treatment can be given either locally or generally to a child of 2½ years suffering from eczema? The lesions are present on the flexor aspect of both legs (in popliteal space), and also on the flexor aspect of elbows and wrists. Lesions are areas of redness and at times covered with scales, at present dry. Various ointments have been tried without any success. The child is well fed, looks well, and has no other defects.*

A.—The variety of eczema described is met with in children of an allergic disposition. General treatment recognizes their highly strung make-up and aims at a placid environment. Cod-liver oil may be given with advantage, and in many cases residence by the sea, and, in suitable weather, sea bathing, are beneficial. A 6% crude coal-tar paste is usually well tolerated, but should be employed only for a limited time. In view of the nervous make-up, attempts at desensitization are best avoided.

LETTERS, NOTES, ETC.

Thumb-sucking

Mr. W. STUART THOMSON, L.D.S., L.R.C.P.Ed. (Edinburgh), writes: With reference to the treatment suggested for the habit of thumb-sucking in your issue of Feb. 19 (p. 277), I should like to criticize very strongly the advice that the child be given a sweet to chew before going to sleep. I quite appreciate that our knowledge of the cause of dental caries is incomplete. Nevertheless, I believe that the large majority of dental surgeons who have studied this subject are agreed that the principal activating cause (or even sole activating cause) of dental caries is the lodgment of fermentable carbohydrate around the teeth. The very worst possible time for carbohydrate to be lodged around the teeth is when the subject is asleep and Nature's cleansing mechanism is at a minimum. Need I say more except to admit that I regret I am unable to offer a suitable substitute for the bedtime sweet?

Treatment of Sciatica

Dr. E. BRAUER writes from Spennymoor, Co. Durham: With great interest I have read Sir Arthur Hurst's article on the treatment of sciatica. To the measures enumerated, however, I would like to add one which I have employed with a very high degree of success indeed. It is that of vitamin B_1 injections. I have given vitamin B_1 in all cases of what I diagnosed as neuritis—facial, intercostal, etc.—and since I regarded sciatica, correctly or not, as neuritis I have used it for this condition as well. I have given it near or far away from the painful region, in the arm or leg, and have nearly always seen good results. Such results, I think, are more than simply due to faith in the treatment; owing to very poor facilities in this area for physical therapy, such as radiant heat, etc., I have not combined this treatment with any of these measures, so that the results cannot be attributed to them. Nor did I make the patient usually rest in bed, except in very severe cases and then only for 2 to 3 days. The results were very rapid, and the patients were fit for work within a fortnight to 4 weeks from the onset of the sciatica. I believe that all cases of what I might call idiopathic sciatica respond to vitamin B_1 therapy; those which showed no improvement at all I regarded as due to causes mentioned by Sir Arthur Hurst, such as prolapse of the nucleus pulposus, etc. I must mention that I find vitamin B_1 in the treatment of neuritis only effective when given parenterally. If given by the mouth the active antineuritic principle seems to be very much diminished if not almost lost in the alimentary canal. To obtain quicker results I have recently used the concentrated ampoules of 25 mg. per c.cm., giving 3 to 6 injections daily or on alternate days.

Infectious Jaundice: A Correction

Dr. A. M. MCFARLAN writes: I find that in your issue of April 1 your report of the discussion on the aetiology of infectious jaundice quotes me as having said: "The laboratory studies included various examinations which excluded the possibility that it was an outbreak of virus disease." This is of course nonsense, and I can only suppose that your reporter misheard what I said about examinations excluding Weil's disease and common bacteriological infections of respiratory or alimentary tracts.